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DEVELOPING AN INDIVIDUALISED EXERCISE INTERVENTION FOR HIP AND KNEE OSTEOARTHRITIS

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

Declaration

I hereby confirm that this thesis is an original research that is composed by me. This work has not been submitted for any other degree or qualification. Authors and works to which reference has been made are entirely acknowledged.

The research, data collection and analyses in this thesis were conducted by me. Supervision and guidance were provided from the supervisory team; Dr Michelle Hall, Professor Weiya Zhang, Professor Michael Doherty and Professor Abhishek. In addition, assistance was received from Dr Siew-li Goh in collaborating with her database on exercise studies for osteoarthritis, and from Burak Kundakci and Ayah Ismail for independent validation of the systematic review (search, screening, risk of bias assessment and quality of intervention description). Technical support and guidance in using STATA software and Microsoft Access was received from Subhashisa Swain and Abasiama Obotiba.

Abstract

Background

Osteoarthritis is a prevalent chronic musculoskeletal condition and is a leading cause of disability worldwide. Non-pharmacological interventions are recommended as first-line of treatment among which exercise is acknowledged as the core intervention for people with hip and knee osteoarthritis. However, there is a need to optimise the effects of therapeutic exercises and improve long-term adherence to it. Therefore, international guidelines recommend individualisation of exercise prescription.

Objectives

The overall aim of this research project is to develop an optimal, individualised exercise package for people with hip or knee OA. In order to achieve this aim, the studies in this thesis aimed to achieve the following objectives:

1. To evaluate the current evidence for individualised exercise interventions for hip and knee OA using a systematic review.
2. To generate a consensus of opinion from a panel of healthcare professionals and patients as to the optimal strategies for individualising exercise interventions for OA using Delphi consensus methodology.

3. To develop a protocol for an individualised exercise programme for knee OA.
4. To test the acceptability of delivering an optimal IE intervention for people with knee OA.

Methods

The project involved three stages with different methodology in each stage. First, reviewing available evidence on individualised exercise and comparing its effects to usual care and non-individualised exercise. This was done by conducting a systematic review with conventional meta-analysis and network meta-analysis. In this review, all individualised exercise studies for hip and knee OA were identified from inception until April 2020. Risk of bias assessment and quality of intervention description of identified studies were assessed. In addition, detailed methods of how exercise was individualised were identified and summarised. Meta-analysis was then used to compare the effect of individualised exercise versus usual care and a network meta-analysis was used to indirectly compare effects of individualised exercise versus non-individualised exercise using a common comparator (usual care).

Second, a consensus of opinion from a panel of healthcare professionals and patients was achieved by conducting a Delphi exercise and stakeholder meetings. The Delphi involved identifying experts in the field

of exercise and OA, and then obtaining their opinions on the optimal strategies for individualising exercise interventions in an anonymised voting system. This was followed by two stakeholders' meetings involving a variety of healthcare professionals and patients to discuss and obtain more views on how to optimally individualise exercise.

Third, an individualised exercise intervention for OA was developed by combining the results of the first two studies. Then, an acceptability study protocol was completed to test the acceptability of delivering the developed intervention. Ethical approval and recruitment stage was completed for this study, however, the whole project was halted due to pandemic national lockdown.

Results

The systematic review identified 17 individualised exercise studies that met the inclusion criteria. The conventional meta-analysis included 8 studies comparing individualised exercise to usual care. Individualised exercise was better than usual care in pain and function outcomes while no significant difference was noted in performance and quality of life outcomes. These results should be taken with caution as the level of heterogeneity was considerably high.

The network meta-analysis showed that the effect size of individualised exercise was better than non-individualised exercise. However, 95% confidence intervals were overlapping, meaning that the difference between these interventions was not significant. The analysis also provided probability ranking score that indicated that individualised exercise is overall the best intervention among the three interventions included (individualised, non-individualised exercise and usual care).

The Delphi study identified 37 different individualisation factors that should be considered when individualising exercise for people with OA. These factors went through two rounds of anonymous voting. The voting resulted in acceptance of 24 items with agreement levels higher than 75%. The stakeholders' meetings resulted in 30 opinion statements that supported and gave context to the factors voted in by the Delphi panel.

The results of the SR and stakeholders' opinions were combined together with evidence from the literature to develop an optimised individualised exercise intervention. Four individualisation factors were chosen to be the focus of intervention protocol: the main symptomatic complaint, the patient's goals, baseline physical capabilities and illness perceptions. These factors were used to constitute an individualised exercise intervention for people with knee OA to be tested in an acceptability study.

Conclusion

Results of this study has demonstrated that IE is beneficial for people with hip and knee OA. IE is significantly better than usual care and is potentially superior to NIE. However, Individualising exercise is a complex procedure and has multiple interacting components that affect its outcomes such as patients and exercise characteristics. IE is poorly described in current RCTs and needs further trials to understand optimal ways of providing IE intervention. The Delphi consensus has identified 24 important individualisation factors that could be considered when prescribing and individualising exercise. Developing a complex intervention is an ongoing process, and the results detailed in this study constitute a part of this process. Further research and trials are warranted to continue the development and optimisation of IE intervention for people with hip and knee OA.

COVID-19 Pandemic impact statement

The pandemic caused by the spread of the COVID-19 virus has directly or indirectly affected everyone. Personally, the national lockdown measures had impacted me on many levels. As my wife and I are current PhD students who had to work from home and take care of a four-year-old child, the lockdown has significantly increased caring responsibilities during the lockdown period. In addition, all of us were affected by the virus in the early stages of the pandemic. The impact on my mental health and physical wellbeing was profound.

The lockdown measures have also directly impacted my research progress. After obtaining ethical approval and completing the recruitment stage of the acceptability study, the project was suspended suddenly due to safety regulations. Later on, after discussions with the supervisory team regarding this issue, we decided to add new elements to the PhD project instead. I had to update the systematic review and conduct a network meta-analysis.

Adjusting to a new plan and learning a new complex methodology during such a difficult period was challenging. However, holding regular meetings with my principal supervisor and the supervisory team provided appropriate guidance and reassurance to overcome these difficulties.

Additionally, communication with peers suffering from the same situation was also a good source of motivation and support.

Moreover, flights restrictions related to COVID-19 has impacted me seriously. As restrictions were getting lift-off by the end of 2020, I travelled back to my home country (Saudi Arabia) for what I expected to be a short holiday. However, due to the emergence of a new variant (Delta variant), travel to the UK from Saudi Arabia was banned. My return flight to the UK was suspended until March 2021, with additional self-isolation for fourteen days had caused a severe delay in my work progress.

List of presentations and publications

Presentations

1. EULAR Annual European Congress of Rheumatology (Virtual congress, June 2020): Individualised Exercise Intervention for Hip and Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials (poster presentation).

Other publications during the period of this thesis

1. Yaseen, K., Hendrick, P., Ismail, A., Felemban, M. & Alshehri, M. A. 2018. The effectiveness of manual therapy in treating cervicogenic dizziness: a systematic review. Journal of Physical Therapy Science, 30, 96-102.
2. Alshehri, M. A., Alhasan, H., Alayat, M., Al-Subahi, M., Yaseen, K., Ismail, A., Tobaigy, A., Almalki, O., Alqahtani, A. & Fallata, B. 2018. Factors affecting the extent of utilization of physiotherapy services by physicians in Saudi Arabia. Journal of Physical Therapy Science, 30, 216-222.
3. Ismail, A., Moore, C., Alshishani, N., Yaseen, K. & Alshehri, M. A. 2017. Cognitive behavioural therapy and pain coping skills training for osteoarthritis knee pain management: a systematic review. Journal of Physical Therapy Science, 29, 2228-2235.

4. Namnaqani, F. I., Mashabi, A. S., Yaseen, K. M. & Alshehri, M. A. 2019. The effectiveness of McKenzie method compared to manual therapy for treating chronic low back pain: a systematic review. Journal of Musculoskeletal and Neuronal Interactions, 19, 492.
5. Khoja, O., Taylor, A., Koculu, E., Alshehri, M. & Yaseen, K. 2020. A systematic review on the effectiveness of cognitive functional therapy for patients with chronic non-specific low back pain. Physiotherapy, 107, e39.
6. Spence, N., Rodrigues, N. C., Nomikos, P. A., Yaseen, K. M. & Alshehri, M. A. 2020. Inter-rater reliability of physiotherapists using the Action Research Arm Test in chronic stroke. Journal of Musculoskeletal and Neuronal Interactions, 20, 480.
7. Obotiba, A., Swain, S., Kaur, J., Yaseen, K., Doherty, M., Zhang, W. & Abhishek, A. 2021. Synovitis and bone marrow lesions associate with symptoms and radiographic progression in hand osteoarthritis: a systematic review and meta-analysis of observational studies. Osteoarthritis and Cartilage.

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List of Abbreviations

ACR	American College of Rheumatology
ACSM	American College of Sports Medicine
BMI	Body Mass Index
CI	Confidence Interval
ES	Effect Size
EULAR	European League Against Rheumatism
GP	General Practice
IE	Individualised Exercise
IPQ	Illness Perception Questionnaire
K/L	Kellgren and Lawrence
KOOS	Knee Injury and Osteoarthritis Outcome Score
KPIC	Knee Pain and Related Health in the Community
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIE	Non-individualised Exercise
NRS	Numeric Rating Scale
OARSI	Osteoarthritis Research Society International
PPI	Public Patient Involvement
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROM	Range of Motion

SD	Standard Deviation
SMART	Specific Measurable Actionable Time bound
SUCRA	Surface Under the Cumulative Ranking Curve
TIDieR	Template for Intervention, descriptor and replication
UK	United Kingdom
US	United States
WHO	World Health Organization

Chapter 1. Introduction and Background

1.1 Osteoarthritis

Osteoarthritis (OA) is an important, worldwide healthcare burden that affects a significant proportion of the population (Lawrence et al., 2008). OA is one of the leading causes of disability in older adults and is, by far, the most common type of arthritis (Lawrence et al., 2008). This chronic condition can affect any synovial joint but the symptomatic sites that have been the most studied to date are the knees, hips, and hands (Dulay et al., 2015, Loeser et al., 2012, NICE, 2014).

1.1.1 Definition and nature of osteoarthritis

OA may be defined according to a number of different viewpoints. Pathologically, OA is restricted to diarthrodial (synovial) joints and can be defined as the combination of focal narrowing of the hyaline cartilage together with bony remodelling and marginal osteophyte formation (Sellam and Berenbaum, 2010). Other changes include synovial and capsular hyperplasia, and atrophy and fibrosis of muscles that act over the joint (Loeser et al., 2012). From a radiographic perspective, focal joint space narrowing, bony remodelling and marginal osteophyte formation are the main features observed (Loeser et al., 2012).

Our understanding of OA has evolved over time. Previously, OA was regarded as purely an age-related, degenerative “wear and tear” condition. However, the focus is now shifting towards a greater emphasis on metabolic and inflammatory changes, as well as biomechanical factors in pathogenesis. This process serves as a built-in repair process of joints, (not inevitable wear and tear that inevitably just gets worse) (Doherty et al., 2016a). Furthermore, although the main focus of interest was previously on cartilage it is now recognised that changes are observed in all the tissues that comprise the joint including hyaline cartilage, fibrocartilage, bone, synovium, capsule and muscle (Doherty et al., 2016a).

The presence of OA in joints does not always cause symptoms such as pain, tenderness, and loss of flexibility. However, even if it is accompanied by symptoms, these symptoms can be variable and intermittent and even resolve completely (Felson et al., 1987, Hannan et al., 2000). The resolution or persistence of symptoms, however, is often not correlated with structural changes, which usually persist and stabilize (Hannan et al., 2000, Dieppe, 2004). Generally in OA, the correlation between the severity of structural change and the severity of symptoms varies between joints. (Hannan et al., 2000, Dieppe, 2004). Sometimes structural changes appear to be severe while pain and other symptoms are relatively mild, while in other instances, symptoms are severe while only moderate

structural changes are noted. In light of that, it is recommended for clinical practice to consider the changes in the joint structure and the changes in symptoms, that is, to distinguish the “OA disease” from the “OA illness” (Lane et al., 2011).

1.1.2 Classification

1.1.2.1 *Imaging*

Radiographic assessment using conventional x-rays is the usual imaging technique used to assess degree of OA. Using radiographs in clinical assessment and clinical trials is common because it is cost-efficient, widely available and easy to use. Additionally, the presence of recognised grading system for radiographic assessment makes more preferable.

In 1957, Kellgren and Lawrence (KL) presented one of the most commonly used assessment tools to help classify OA severity. The KL scale classified the radiographic features of OA into five grades: none, doubtful, minimal, moderate and severe (Table 1-1). This grading system focuses purely on structural changes that appear on radiographs (Figure 1-1). It was, however, criticised for a number of reasons such as giving too much weight to the presence of osteophytes with less attention to the joint space narrowing (McAlindon et al., 1992). One common criticism of the grading scale is its utilization in detecting the progression of OA. Spector and

Cooper (Spector and Cooper, 1993) criticised the criteria for being non-linear, assuming that structural features of OA happen all together rather than independently.

Table 1-1. Kellgren and Lawrence diagnostic criteria

Grade	Description
0	Normal
1	Doubtful narrowing of joint space, possible osteophyte
2	Definite osteophyte, possible narrowing
3	Moderate multiple osteophytes, definite narrowing, some sclerosis, possible deformity of bone ends.
4	Large osteophytes, marked narrowing, severe sclerosis, definite deformity of bone ends

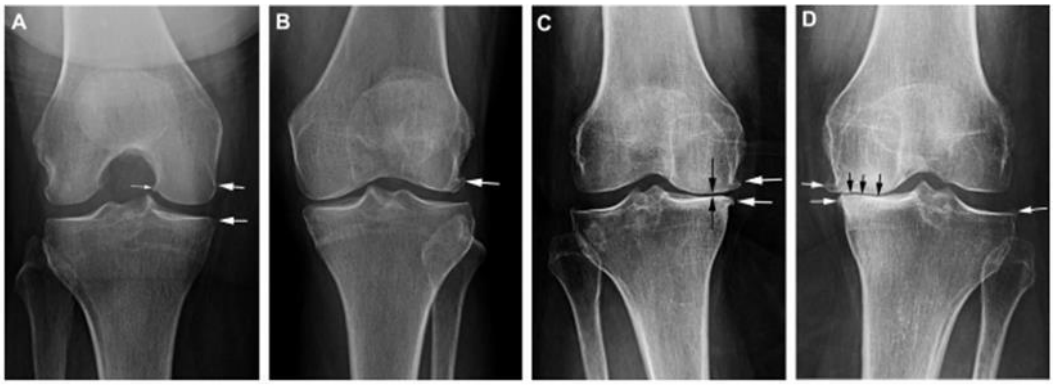


Figure 1-1. Kellgren-Lawrence grading based on presence of osteophyte

A: Grade 1-Minimal osteophytes. B: Grade 2- Definitive osteophyte
C: Grade 3- Multiple osteophytes and definite joint space narrowing
D: Grade 4- Large osteophytes and obliteration of joint space.

Magnetic resonance imaging (MRI) is another imaging technique that is known to be more robust as it captures abnormalities of soft tissues (e.g. synovial hypertrophy, joint effusion), cartilage and bone marrow oedema. However, there is not a recognised MRI-based OA assessment tool that provides cut-off criteria for confirm absence or presence of OA (Hunter et al., 2015).

1.1.2.2 ***Clinical classification***

The American College of Rheumatology (ACR) presented an assessment tool that is often used to determine the presence of clinical or symptomatic OA (Altman et al., 1986). Pain was the major element for inclusion, in addition to other elements such as crepitus, morning stiffness for <30 minutes, age (>50), enlargement and tenderness in the bone as well as no palpable warmth (Altman et al., 1986). Regarding hip OA, Altman et al (1991) provided a scale that is specialized to hip assessment. Elements of inclusion for hip assessment are slightly different to the ones in the knee scale. Hip OA sign include presence of hip pain, with the addition limited internal rotation (<15 degrees) and morning stiffness for ≤60 minutes (Table 1-2).

Table 1-2. American College of Rheumatology (ACR) assessment criteria for hip and knee osteoarthritis

Knee	Hip
Knee pain + At least 5 of these 9 signs: • >50 years old • Morning stiffness <30minutes • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth • RF 1:40 • ESR < 40mm/hr • Synovial fluid = clear, white blood cell count <2000/mm3	Hip pain + • Hip internal rotation <15 + One or more of the following: • ESR ≤ 45mm/hr • hip flexion ≤115 • Hip internal rotation ≥15 + • Pain on hip internal rotation + • Morning stiffness ≤60 minutes + • >50 years old

ESR = erythrocyte sedimentation rate. RF = Rheumatoid factor.

1.1.3 Epidemiology of osteoarthritis

1.1.3.1 *Prevalence*

OA is a very prevalent medical condition; it is reported that in the United Kingdom (UK), around 30% of the population over 45 years sought medical care for OA treatment (Jordan et al., 2007). In the United States, an estimate from 2005 put nearly 9% of the population (27 million) as suffering from symptomatic OA (Lawrence et al., 2008).

A recent study has shown that in the UK prevalence of OA in women (12.8%; 95% CI 12.8-12.9%) was higher than in men (8.6%; 95%CI 8.5-8.7%) in 2017 (Swain et al., 2020b). The study has also identified an age-related increasing trend of OA prevalence. The prevalence trend shows a sharp increase at age 45-49 for men and age 40-44 for women and continues to increase until the 80s. Peak prevalence for women is 47%, while peak prevalence for men is 35% (Swain et al., 2020b).

Furthermore, OA prevalence varies according to the joint site. In the overall population, the highest prevalence of OA in all joints was knee (2.9%, 95% CI 2.7-2.9%), hip OA was second most prevalent (1.5%, 95%CI 1.4-1.5%) while prevalence of wrist and hand OA (0.5%, 95%CI 0.5-0.5%) and ankle and foot OA (0.3%, 95% CI 0.3-0.3%).

1.1.3.2 *Incidence*

Trends of OA prevalence is showing a concerning increase over time. In the UK, between 1992 and 2013, the incidence of OA in adults over 45 years has shown an increase reaching 40.5/1000 person-years (Yu et al., 2017). The study reported that the overall incidence rate was broadly stable in the period between 1992 and 2000. However, a steep increase was noted in the years after 2000 (Yu et al., 2017).

Furthermore, a UK based study has shown that in 2017 OA cases in people under 30 years of age are relatively rare (0.08 per 1000 person-years) (Swain et al., 2020b). However, the age-related incidence rate has increased with advancement of age which peaked at age of 75-79 (27 per 1000 person-years) (Swain et al., 2020b). Additionally, knee OA incidence was highest among other joints (2.3; 95% confidence interval (CI) 2.2 to 2.4 per 1000 person-years) while hip incidence rate was (1.1; 95% CI 1.1 to 1.2 per 1000 person-years).

1.1.3.3 *Healthcare Burden*

OA causes a huge burden on healthcare systems and societies. Both hip and knee OA significantly affect people's quality of life as a result of pain and stiffness, which adversely affect mobility and productivity (Guccione et al., 1994). Hip and knee OA were ranked 11th on the list of highest

contributors to a global disability, according to the Global Burden of Disease (GBD) report (Roberts et al., 2019). In addition, the world health organisation (WHO) (2021) reported that OA constitutes the third most contributor to the overall burden of musculoskeletal conditions.

In the UK, musculoskeletal conditions have a considerable impact on the economic system. In the financial year of 2014-2015, costs of hospital admissions related to musculoskeletal conditions were 4.1 billion sterling pounds (DOH, 2016). Additionally, other indirect costs are also substantial. For example, in 2015-2016, the labour force survey reported that 8.8 million working days were lost due to musculoskeletal conditions (Ingram and Symmons, 2018, DOH, 2016).

In the United States, OA is second to ischemic heart diseases in causing work-related disabilities in men over 50 years old. It is also estimated that 44 million healthcare consultations and 3.8 million days of hospitalization in the United States per year are related to OA (Dunlop et al., 2003).

Furthermore, OA is the most common cause of joint replacement surgeries worldwide. OA was the leading cause of 93% of all hip replacement surgeries and 97% of all knee replacement surgeries in 2010. Total joint arthroplasty is a costly procedure (Chen et al., 2012). In the UK, the operation costs vary from trust to trust, and its price depends mainly

on the duration of hospital stay after the surgery (Chen et al., 2012). In 2010, In 2010, the overall estimated total knee replacement costs were 426 million sterling pounds and for hip replacement 426 million sterling pounds (Chen et al., 2012). This causes a substantial burden on the UK health system, and yet the number of surgeries and its costs continue to increase year by year.

Unfortunately, despite all the advances in research, defining and treating OA is still challenging for practitioners. It is a heavy burden placed on communities, and there remains a need to achieve advances in the quality of medical care.

1.1.4 Factors influencing the development and progression of osteoarthritis

OA is a common complex condition with variable interactions between genetic, constitutional and environmental risk factors. These factors can be divided into being either non-modifiable (e.g. age and gender) or modifiable (e.g. obesity, nutrition and injury prevention) risk factors (Johnson and Hunter, 2014). This section will provide an overview of the main factors thought to be related to the development and progression of OA.

1.1.4.1 ***Genetics***

The potential risk of developing OA is strongly related to genetics, accounting for around 40% of knee OA and around 60% of hip OA (Spector and MacGregor, 2004). Examples of these genetic factors may include genes involved in joint morphology and alignment, muscle balance and body mass index (BMI) (Hogervorst et al., 2012, Spector et al., 1996, Zhai et al., 2005). Heritability of OA varies according to joint site. A study by Spector and MacGregor (2004) showed how genes contribute to OA development in the cervical spine, lumbar spine, hip, knee and hand (Figure1-2). Among these joints, the knee was the least affected by genetic factors (45%), followed by the hip (60%), while OA of the spine had the highest incidence related to hereditary factors.

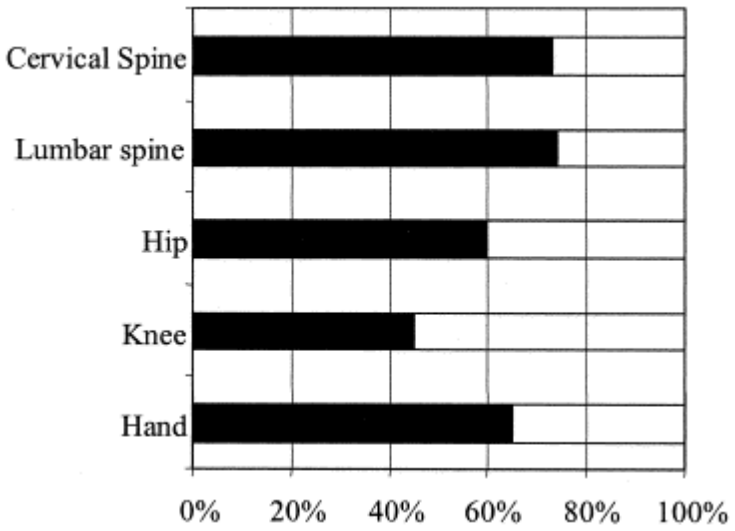


Figure 1-2. Gene contribution to OA development by region (MacGregor, 2004)

1.1.4.2 *Constitutional risk factors*

Constitutional (or systemic) factors affecting OA are mainly related to age, gender, weight, nutrition, and structural deformities. Evidence from a number of population-based studies show that OA has a strong relationship to age (Leyland et al., 2012, Neogi and Zhang, 2013). OA risk increases steeply after age 50, according to recent studies (Yu et al., 2015, Cross et al., 2014). However, that does not imply that OA is an inevitable consequence of aging (Doherty et al., 2016b). In regards to gender, women seem to have an overall greater risk of having OA than men (Jordan et al., 2009). Not only this, but some studies suggest that OA in women tends to be clinically and radiographically more severe than in men (Dagenais et al., 2009, Srikanth et al., 2005, Keefe et al., 2000).

Another risk factor for OA is higher body weight. There is consistent evidence that higher BMI increases the risk of lower-limb OA. A Swedish population study revealed that the relative risk of developing knee OA is 8.1 in people with BMI >30 (Lohmander et al., 2009). Being overweight increases the risk of developing the condition as well as the risk of radiographic progression (Felson et al., 2000). It was also found to be a strong predictor of increased pain and the need for total joint replacement (Muthuri et al., 2011, Franklin et al., 2009). Obesity is a global healthcare care problem that is increasing in prevalence and is one of the most important modifiable risk factors for OA (Hruby and Hu, 2015). Therefore,

it is highly likely that the prevalence of OA will increase in the future (Swain et al., 2020b, Yu et al., 2017).

1.1.4.3 ***Local (Joint) risk factors***

Local or joint level risk factors related to OA are joint overuse, injury and reduced muscle strength (Johnson and Hunter, 2014). These factors are considered an important predictor of the condition. Even though a moderate level of exercise is known to be healthy for joints (Shrier, 2004), joint overuse and repetitive occupational stress on joints can be harmful. For example, occupational overload on hand joints was found to be highly correlated to hand OA (Croft et al., 1992) and there is an increased risk of lower limb OA in workers involved in lifting and bending activities (Felson et al., 1991, McWilliams et al., 2011).

There is still no clear cut-off point to define how occupational stress differs from sports-related physical stress. That could be attributed to the diversity and complexity of sports activities, which may present a challenge to identifying the direct relationship to exercise. A recent, systematic review published by Timmins et al (2017) investigated the relationship between running and osteoarthritis. The study reported low-quality evidence suggesting a positive relationship between running and OA diagnosis and a negative association with joint replacement surgery. Another study

investigated the prevalence of knee OA in ex-footballers in comparison to males from the same age group from the general population (Fernandes et al., 2017a). This study found that ex-footballers are at 2-3 times higher risk of suffering from knee OA outcomes (e.g. pain and total knee replacement).

Overt joint injury to the knee and hip are another important risk factor for developing OA (Lohmander et al., 2004). This was also evident in a 36-year-prospective study done by Gelber et al. (2000) that reported that those with a history of injury had a higher relative risk (RR= for knee 8.72, 95% CI 4.29-17.7, hip= 4.25, 95%CI 0.55-32.60) of OA than those with no injury.

Furthermore, it is common for patients with OA to have deficits in muscle strength, activation and proprioception, which can be a result of pain avoidance and fear of movement (Bennell et al., 2013). On the other hand, muscle weakness can be a predisposing factor for developing lower limb OA (Bennell et al., 2013). A study by Petterson et al (2008) revealed that the cross-sectional area of the quadriceps was 12% smaller in the affected side when compared to the non-affected limb of the same person with late-stage preoperative knee OA. However, this could be attributed to the fact that, in their daily activities, patients tend to utilize their non-symptomatic side more to avoid pain. That can therefore strengthen and

enlarge the muscles of the contralateral limb. Additionally, a relationship exists between muscle strength and the progression of OA. Weakness of muscle can have negative effects on the structural and symptomatic progression of the condition (Slemenda et al., 1997), while improved strength is directly associated with the reduction of pain and improvement in function (Bennell et al., 2013).

Although it often overlooked, changes in joint muscles as a result of OA are crucially important. Joint function is reliant on the integrity of the muscles surrounding the joint which is often affected by OA (Hurley, 1999). A longitudinal cohort study by Sharma et al (2003) showed that people with knee OA suffered from weakness in quadriceps and hamstrings in addition to decreased proprioceptive acuity. The study also reported that this changes in muscles quality was correlated with decrease in physical function. However, it is still unclear whether changes in muscles integrity is attributed to joint disuse due to pain or is caused by the inflammatory changes of OA.

1.1.5 Pathology of osteoarthritis

OA has been presented as a group of overlapping conditions with multiple person dependant aetiologies (Brandt et al., 2008, Weinans et al., 2012). Multiple pathological models described OA pathogenesis differently,

however, the overall agreement is that once the bone-cartilage interface of the joint is disturbed, the progressive cascade of OA starts. This leads to an active repair process that dynamically involves all tissues and structures surrounding the joint surface. This process can be referred as a ‘wear, tear and repair’ rather than ‘wear and tear’ process (Shelton et al., 2016). The repair process embodies the aetiological role of initial mechanical insult, which triggers inflammation and mechanical adaptation of joint tissues in order to compensate for the damage done to the joint (Shelton et al., 2016). The remodelling process that occurs in the joint leads to development of new bone and altered joint shape and the biomechanical changes often compensate for the joint insult(s) that initiated the whole process. However, in some cases the repair process fails due to some individual risk factors and/or continuous microtrauma causing overwhelming damage to the joint.

1.1.5.1 ***Changes in cartilage***

Changes occur in many tissues from an early stage of OA, and can be triggered by initial damage in articular cartilage, bone, meniscus (Loeser, 2010, Van Dijk et al., 2010, Madry et al., 2010). In this situation, number of chondrocytes increase as well as its activity leading to production of more matrix components than usual. However, joint failure may occur in case of failure of chondrocytes in maintaining balance between synthesis and

degradation of components of the extracellular matrix (Goldring, 2009, Loeser, 2010). This extracellular matrix is formed of two components, the tissue fluid and the framework of structural macromolecules that contains glycoproteins, type II collagen fibres, proteoglycans and non-collagenous proteins. These components form a highly organised matrix which gives tensile strength to the cartilage (Buckwalter et al., 2005). However, any imbalance may occur in this extracellular matrix and results in increased water content and decreased proteoglycan that leads to decreased synthesis of type II collagen and increased breakdown of pre-existing collagen. This eventually leads to weakening of collagen network which can consequently lead to an increase in chondrocytes, which are essential to maintain remodelling-compensatory mechanisms. Therefore, loss of chondrocytes can disturb the natural repair process of the joint (Buckwalter et al., 2005).

In early stages of OA, degenerative changes in the cartilage mostly happens in focal areas of the cartilage due to mechanical forces. However, progressive changes can be observed in surrounding areas and other joint surface structures as OA advances (Pritzker et al., 2006).

1.1.5.2 *Changes in bone and subchondral region*

Changes in the subchondral region such as osteophytes formation, sclerosis and cyst formation are typical in osteoarthritis. Analysing bones from individuals with severe OA shows reduction of mineralisation content and increase in density volume of bone (Fazzalari and Parkinson, 1997, Grynpas et al., 1991). This reaction from the body is often seen with any cause of cartilage damage (Carlson et al., 1996, Matsui et al., 1997). The changes in subchondral bone play an important role in more evenly distributing the weight-bearing force in order to protect the joint structures from damage (Weinans et al., 2012).

Furthermore, bone marrow lesions (BMLs) are among the pathologies that occur in bony structures in people with OA. BMLs are a bone abnormality caused by focal osteonecrosis and excessive fibrosis that can be detected by magnetic resonance imaging (MRI). BMLs are often associated with joint pain. A study by Hunter et al (Hunter et al., 2008) found that over 75% of people with symptomatic OA have had BMLs while only 30% of asymptomatic OA had BMLs. Additionally, BMLs were detected in people with abnormal knee biomechanics and joint mal-alignment causing progressive narrowing of joint space (Felson et al., 2001). However, it is still debatable whether BMLs develop in response to changes in the cartilage or if it occurs prior to changes in articular cartilage (Aspden, 2008).

1.1.5.3 *Changes in synovium and peri-articular structure*

OA is condition that affects the whole joint, not just the cartilage-bone interface (Loeser et al., 2012). Degenerative and regenerative changes occur in subchondral bone as well as synovitis, degeneration of menisci and ligaments, and hypertrophy of articular capsule (Martel-Pelletier et al., 2008). The main changes often seen in synovial level with OA are: thickening of synovial capsule, fibrosis, synoviocytes activation and infiltration of lymphocytes such as B-cell, T-cells and plasma cells (Roach et al., 2007). Cytokines and chemokines, which are inflammatory mediators, increase in synovial fluid causing synovitis (Loeser et al., 2012). Although synovitis can occur in early stages of OA, it is more prevalent in advanced stages of OA (Krasnokutsky et al., 2011). Thus, synovitis contributes to the severity of OA and rate of degenerative changes. Moreover, synovitis was found to be a potential predictor of development of symptoms in OA with odds ratio (OR) of 9:2, (95% CI 3:2–26:3) and a predictor of cartilage loss with OR of 2:7, (95% CI 1:4–5:1) (Scanzello and Goldring, 2012, Roemer et al., 2011).

In addition to changes in synovium, changes in menisci are common in knee OA. Joint's meniscus is important to maintain the integrity of movement in the joint surface, while it has lesser role in development of

symptoms (Hunter et al., 2013). Meniscal tears are prevalent in people with knee OA either non-symptomatic (67% in mean age of 65) or symptomatic (91% in mean age of 65) (Bhattacharyya et al., 2003). Thus, it is argued that there is no correlation between development of symptoms and meniscal tears in OA (Bhattacharyya et al., 2003).

1.1.5.4 *Inflammatory process in osteoarthritis*

Inflammatory response in human body is a protective mechanism that occur as a response to tissue damage, whether this damaged was caused by traumatic, pathogenic or toxic injuries (Benelli et al., 2006). Pro and anti-inflammatory molecules control the inflammatory process. These molecules act together to regulate chemotaxis, migration and proliferation mechanisms that involves removal of damaged tissue and formation of new tissue to facilitate repairing the damaged tissue (Benelli et al., 2006). OA is a complex disease that involves multiple pathologic mechanisms that include release of inflammatory mediators released by joint structures such as bone, cartilage and synovium (Loeser, 2010, Kapoor et al., 2011).

1.1.5.4.1 Localised biomarkers

Focal cartilage degradation is one of the main features of OA. Products of cartilage breakdown can be detected before cartilage damage can

diagnosed by arthroscopy or magnetic resonance imaging (MRI) (Pauli et al., 2011, Ayral et al., 2005). Biochemical markers are known to be associated with OA's development and severity of symptoms (Sokolove and Lepus, 2013).

Joint overuse and microtrauma often lead to development of chronic inflammation that contributes to development of a self-sustaining cycle of tissue damage, inflammatory response and repair (Scanzello et al., 2008).

1.1.5.4.2 Systemic and metabolic triggered inflammatory changes

Development and progression of OA is correlated with the presence of inflammatory mediators. The mediators are either originated from local joint cells or body tissues outside the joint (systemic source) (Ayhan et al., 2014). Comparing people with OA to healthy individuals showed presence of higher levels of inflammatory mediators in people with OA than in healthy subjects (Fernández-Puente et al., 2011, Attur et al., 2012).

Attur et al (2012) have investigated the gene expression profiles of peripheral blood leukocytes (PBLs) in people with OA in a cluster analysis. The study showed that one group of OA subjects had increased level of IL-1β signature while the other group had normal gene expressions.

Interestingly, the group with higher IL-1β had more severe symptoms of OA and worse radiographic condition than those with lower IL-1β.

Adipokine, which is an inflammatory marker linked with obesity, is an inflammatory marker that reaches joint surfaces through vessels in subchondral bone (Berenbaum, 2013, Pottie et al., 2006). Presence of adipokine is correlated with obesity and risk of developing OA in several body joints including the hands (Yusuf et al., 2010). Additionally, presence of adipokine is significantly associated with synovitis (De Boer et al., 2012). These findings indicate that obesity is a risk factor for developing OA, not only due to biomechanical abnormality, but due to inflammatory response as well.

Increased level of lipids and glucose, abnormal changes in vitamin D levels, in addition to complement components such as acute phase proteins, increase production of pro-inflammatory substances such as cytokines and adipokines (Gabay and Kushner, 1999). Therefore, such disturbance to the metabolic systems can lead to development of chronic inflammation triggered by metabolic factors (meta-inflammation) that is closely linked with pathogenesis of OA (Wang et al., 2015).

Presence of chronic systemic inflammation can potentially be a factor that leads to development and/or aggravation of OA. However, this claim has

yet to be confirmed as more experimental and epidemiological studies are needed (Berenbaum, 2013).

1.1.6 Pain in osteoarthritis

Majority of people with OA do not have symptoms (Culvenor et al., 2019). However, for people suffering from symptomatic OA, pain is the most frequently reported symptom. Pain is, according to clinical criteria for OA diagnosis, a major factor for defining the condition. A survey conducted by Murphy et al. (2008) which included 2000 people with symptomatic OA, reported that around 81% of them suffer from pain or limitation with daily activities. Severe pain in advanced OA stages was found to affect mood, sleep and social activities and thus reduces quality of life (Neogi, 2013).

Pain is a complex, subjective experience. Its perception varies from one person to another, and that can be influenced by biological, psychological and social factors (IMO, 2011). Nociceptive fibres exist is tissues with the joint such as periosteum, subchondral bone, joint capsule with its synovial lining, ligaments and muscles. These fibres produce painful nociception signals in response to tissue damage or potential damage (Hunter et al., 2013). Normally, pain is a protective mechanism. However, persistence of pain after the threat is resolved is considered to be maladaptive behaviour (Neogi, 2013). In OA, pain is typically chronic. However, some studies

suggest that the level of pain intensity is not always correlated with structural damage, as the intensity of pain often changes and may resolve completely at times, while structural changes stabilise (Felson et al., 1987, Dieppe, 2004, Hannan et al., 2000).

Besides local structural changes, a variety of factors modulate pain perception in OA patients. For example, genetic predisposition relating to variants related to the endogenous opioid system was found to influence how different people experience pain differently (Zubieta et al., 2001). The extent of the genetic effects is still not clear, especially when compared to other environmental factors (Mogil, 1999).Additionally, coping strategies and catastrophising traits or states are among the factors that affect the reporting of pain levels (Bradley, 2004).

A recent, systematic review concluded that there is a potential positive effect of altering pain coping strategies (e.g. cognitive behavioural therapy) in patients with knee OA (Ismail et al., 2017). However, there is still very limited evidence in this regard and further studies are needed to explore this area (Ismail et al., 2017). Catastrophising or excessive worry about pain is linked to people having more severe OA pain, poorer physical function and poorer quality of sleep (France et al., 2004, Sinikallio et al., 2014, Wideman et al., 2014). Furthermore, anxiety, depression, expectations, prior experience and sociocultural environment are also

factors that significantly influence how people experience pain (Giardino et al., 2003, Mayer and Saper, 2000, Colloca and Benedetti, 2006, Woo, 2010).

Neural plasticity that results from peripheral and/or central sensitisation contribute to severity and chronicity of pain in OA. Hypersensitisations alter sensitivity of primary afferent nerves during the acute and chronic stages of inflammatory response. This makes the body overly sensitive even to normal harmless pressure on the joint surface (Hunter et al., 2013). This is known as peripheral sensitisation. Over time, persistence of this form of sensitisation contribute to development of plastic changes in the central nervous system (central sensitisation) (Woolf and Salter, 2000). Central sensitisation makes the spinal cord's second-order neurons hyper-reactive to signals coming from the peripheral nervous system and it increases the responsiveness to nociceptive stimuli in the somatosensory cortex. Thus, central sensitisation can lead to heightened pain experiences and in some cases sensation of pain in areas that is distant from the original site of insult (Hunter et al., 2013).

1.2 Management of osteoarthritis

1.2.1 International guidelines for managing osteoarthritis management

OA management is challenging, and the current levels of intervention are often seen more as a type of palliative care (i.e. symptom management rather than curative) (Johnson and Hunter, 2014). International guidelines for OA provide generally consistent recommendations regarding OA management. The majority divide OA interventions into either non-pharmacological, pharmacological, or surgical subdivisions. The National Institute for Health and Care Excellence (NICE, 2014) guidelines recommend non-pharmacological interventions including patient education, exercise (both local strengthening and aerobic) and weight reduction if required as core interventions. In addition, Osteoarthritis Research Society International (OARSI) guidelines recommended non-pharmacological as core intervention for all stages of OA severity (Bannuru et al., 2019). Furthermore, Roos et al (2012) also placed non-pharmacological interventions as the first-line of treatment for OA in the hierarchy of interventions they proposed (Figure 1-3).

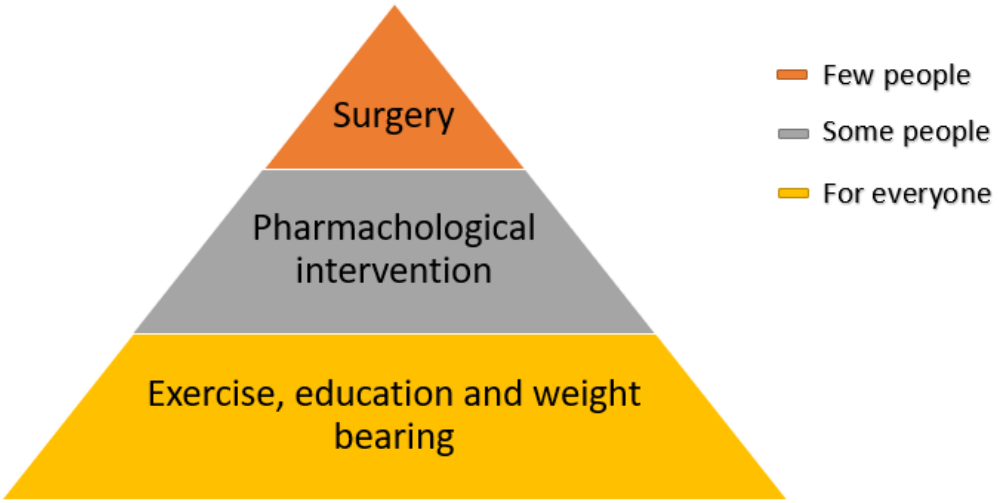


Figure 1-3. Osteoarthritis management options, adopted from Roos et al. (2012)

In terms of pharmacological interventions to date, no treatment can modify or affect the structural changes of OA. Management mainly consists of analgesics that can be administrated orally, topically or by intra-articular injection. These treatments mainly aim to manage pain, and it is recommended that they are purely adjuncts to management and should always be administrated in conjunction with other conservative core interventions (NICE, 2014).

In case of failure of all appropriate conservative and pharmacological interventions, and if the symptoms of OA start to adversely and severely affect the patient's quality of life, surgery may be considered as an treatment option (NICE, 2014). Since joint arthroscopy is no longer recommended, the main surgical option for severe knee or hip OA is total joint replacement (NICE, 2014). Despite the risks and also exposing the

patients to many complications and the possibility of persistence of pain even following surgery, total joint replacement for marked hip and knee OA resistant to medical treatment is considered overall to be an effective intervention that provides good results in most appropriately selected people (Kittelson et al., 2014, Beswick et al., 2012).

1.2.2 Exercise for osteoarthritis

Exercise is a widely used intervention in healthcare and is known to have positive effects on pain and function. Exercise and physical activity are terms used widely in OA literature. Exercise can be defined as a repetitive movement that is planned intentionally to improve or maintain the health of joints or of the general body. Physical activity, on the other hand, is another widely used concept, which is known as any movement produced from the musculoskeletal system that demands energy expenditure (Chodzko-Zajko et al., 2009). Exercise has many beneficial effects both for joint health, such as pain reduction and improving mobility and function, and general health, such as reducing medication intake, physical functioning, mental health and self-efficacy (Roddy et al., 2005a, Miller et al., 2003, Goh, 2018).

Two Cochrane systematic reviews investigated the literature regarding exercise for knee and hip OA (Fransen et al., 2015, Fransen et al., 2014).

The review on knee OA included 54 randomised controlled trials (RCTs) and a total of 5362 participants (Fransen et al., 2015). Forty-four studies reported a significant change in pain intensity and physical function immediately after exercise with moderate effect size (ES) of 0.49 (95% CI 0.39 to 0.59) and 0.52 (95% CI 0.39 to 0.64), respectively. However, only 12 studies reported long-term (longer than six months) results in pain outcome and showed significant improvement but with a small ES of 0.24 (95% CI 0.14 to 0.35). Long-term change in physical function was reported in only 10 RCTs and showed significant improvement with a small effect size (0.15, 95% CI 0.04 to 0.26).

Secondly, a systematic review and meta-analysis that evaluated the evidence regarding exercise for hip OA included 10 RCTs (549 participants) (Fransen et al., 2014). Only five of the included studies recruited patients with purely hip OA, while the other five studies recruited a mixture of hip and knee OA participants. The reviewers concluded that there was a high level of evidence that exercise induces significant improvements in pain and physical function in hip OA patients (Fransen et al., 2014). Additionally, the study reported that long term effects of exercise on pain reduction was sustained for 3-6 months in five RCTs (381 participants). However, it is unclear whether adherence to exercise was sustained or not and if the pain level changed after 6 months.

More recently, a systematic review has looked into the efficacy of exercise intervention on hip and knee OA (Goh et al., 2019a). The study included 77 RCTs involving 6472 participants and concluded that exercise significantly reduces pain and improves function, performance and quality of life of people with OA. These improvements peak at eight weeks. However, it then started to diminish after eight weeks and was no longer better than usual care after 9-18 months. This was attributed mainly to a lack of adherence to exercise.

1.2.2.1 *International recommendations for exercise in osteoarthritis*

Guidelines worldwide universally recommend the use of exercise as a core treatment for OA (Bannuru et al., 2019). The European League Against Rheumatism (EULAR) committee agreed that there is high-quality evidence that exercise has positive effects on OA symptoms (Fransen and McConnell, 2008, Jamtvedt et al., 2008). For knee OA specifically, evidence shows that exercise, in both aerobic and strengthening forms, in different methods of delivery (individualised, group-based or home programs), improves pain and function (Fransen and McConnell, 2008). However, there is less evidence among clinical trials in regard to the effects of exercise in Hip OA Therefore, the effects of exercise are less clear, and strengthening exercise is poorly evaluated. Finally, EULAR guidelines highlighted uncertainty in regard to the dosage and rate progression of exercise intervention.

Furthermore, NICE guidelines recommendation specified that irrespective of age, comorbidity and pain severity both strengthening and aerobic types of exercise should be prescribed. Consistently, OARSI also recommended land-based (ES for pain 0.34, and for function 0.25) exercises for knee OA management in all stages of the condition (McAlindon et al., 2014, Jansen et al., 2011, Bannuru et al., 2019).

1.2.2.2 ***Mechanisms of action***

People with hip or knee OA can achieve multiple biomechanical improvements through exercise (Zeng et al., 2021). Evidence shows that strengthening exercise can lead to effective increase in muscle cross-sectional area and improvements in tendon structure and mechanics (Assis et al., 2015, Bezerra et al., 2012). These studies argue that by achieving biomechanical improvements, exercise can slow down or completely halt cartilage degeneration due to a reduction in the shear force on the joint surface.

Furthermore, multiple studies on rat models have shown that exercise can regulate inflammatory mediators such as IL-1β, caspase-3 and MMP-13, IL-1β, IL-6 and TNF-α (Assis et al., 2015, Vasilceac et al., 2021, Chen et al., 2020). This effect has the potential to halt cartilage degeneration and

slow down the inflammatory process, which improves the general health of the affected joint. For example, a study on a rat model revealed that subjects that perform aerobic exercises (e.g., swimming) in the early stages of OA may be able to delay and minimise the symptoms of OA more than those who start the swimming intervention in the late stages (Hsieh and Yang, 2018).

According to Zeng et al (2021), clinical trials and experiments on animals have shown that exercise has a variety of benefits for people with OA. Those benefits can be summarised in the following main points:

1. Increases muscle cross-sectional area
2. Improves tendon structure
3. Delays (or stops) muscle atrophy
4. Delays osteoarthritic changes
5. Prevents degeneration of the articular cartilage
6. Prevents the loss of subchondral bone
7. Slow down the inflammatory process
8. Reverses synovial cell dysfunction

Additionally, the benefits of exercise for people with OA are not solely biomechanical improvements. Exercise has a significant positive impact on the psychosocial wellbeing of people with OA, psychosocial factors directly affect pain sensation in chronic musculoskeletal conditions. In fact,

a recent systematic review of RCTs has shown that exercise has a beneficial impact on the overall mental health, depression, anxiety and self-efficacy of people with OA (Hall et al., 2019).

The study emphasised that the psychosocial impact of exercise in OA management is important and can significantly affect the outcomes of intervention (e. g., pain and function) (Hall et al., 2019). However, it was concluded that the evidence for these findings was of low to moderate quality, and further research in this regard is required. Additionally, the study highlighted a major limitation in the literature, namely poor reporting of exercise and the potential mediating factors within trials.

It is unfortunate that we still lack understanding in this area, although it is known that these factors may significantly impact the outcomes of intervention. Therefore, there is a need to further investigate the relationship between specific exercise characteristics and psychosocial characteristics and how these factors can be used to maximise the benefits of an intervention.

1.2.2.3 *Types of exercise*

Many different types of exercise have been evaluated in the management of OA. Two specific types of exercise are supported by a considerable body of evidence: local strengthening exercise and aerobic exercise (Juhl et al., 2014, Nijs et al., 2012). However, according to a recent systematic review, there is no clear superiority in regards to the clinical effects of one specific exercise type over others in OA management (Goh, 2018).

1.2.2.3.1 Strengthening exercise

This is a type of exercise during which the muscles are forced to contract against a resisting force, such as an object weight, elastic band or body weight, with the aim of gaining strength. According to Kenney and Wilmore (2015), muscles gain through the process of neuromuscular recruitment of contractile fibres, in addition to the hypertrophy of the muscle fibres that usually results from strengthening exercises.

The rationale for the effects of strength training for OA management is convincing due to the association that exists between muscle strength and OA (Deasy et al., 2016, Øiestad et al., 2015). As previously explained, decreased muscle strength is a risk factor for developing OA pain (Roos et al., 2011). A study by Segal and Glass (2011) suggests that improving the strength of knee extensor muscles can protect from symptomatic (but not

radiographic) knee OA. This could be attributed to the fact that muscle strength improves joint stability, decreases the load on the joint and serves as a shock absorber for the joint (Bennell et al., 2013).

Moreover, the human body's muscles act together in a synchronised pattern to perform actions such as walking and maintaining balance. Therefore, exercising multiple muscle groups is more efficient than focusing on one specific group (e.g. quadriceps) (Fransen et al., 2015, Bennell et al., 2014). Even though strengthening exercise is one of the most commonly used exercise interventions for OA management, its prescription should be made with some sense of judgment considering different patients' phenotypes (i.e. a fit, athletic OA patient is different from an elderly, less fit patient) (Knoop et al., 2011).

The systematic review by Goh et al. (2018) has shown significant improvements with strengthening exercises for both hip and knee OA. The study looked into the relative efficacy of different types of exercise, and concluded that strengthening exercise improves pain in people with knee OA (ES: 0.76, 95%% CI 0.50, 1.02) and in people with hip OA (ES: 0.53, 95%% CI − 0.74, 1.80). The study has also looked in effects of strengthening exercise on outcomes of function, performance and QoL. Similar to effects on pain outcomes, improvements were detected across all outcomes. Overall number of trials included in this analysis was 75

RCTS for knee OA (5208 participants), while for hip OA only 10 RCTs (905 participants) were included. This shows a small number of studies investigating effects on hip OA indicating a need for further studies effects for this condition.

Furthermore, a systematic review in 2014 that examined 47 studies for the effects of different types of exercise in knee OA showed significant improvements with strengthening exercises in pain (ES 0.62, 95% CI 0.45 to 0.79) and function (ES 0.60, 95%% CI 0.37 to 0.83) (Juhl et al., 2014). However, the study's inclusion criteria for intervention were highly heterogeneous and some studies were purely strengthening exercises and others had additional types of exercise alongside strengthening. Another systematic review by Lange et al. (2008) investigated the effects of strengthening exercises for knee OA management. Eighteen studies were included, with a total of 2832 participants enrolled. Of the studies, 50-75% found clinically significant improvements in OA symptoms, functional ability and muscle strength.

1.2.2.3.2 Aerobic exercise

Aerobic exercise such as walking, swimming and cycling are forms of exercise that require the movement of large muscle compartments of the

body in a rhythmic and usually functional manner, sufficient to increase heart rate, breathing rate and oxygen consumption.

The rationale for pain relief during aerobic exercise is related to its multiple central effects including increased endogenous opioid release, increased dopamine and reduced cholecystokinin (Nijs et al., 2012). As endorphins are released, aerobic exercise has an indirect, positive effect on pain sensitivity, psychological wellbeing and sleep quality in OA patients (Nijs et al., 2012, Wang and Youngstedt, 2014). Furthermore, moderate-intensity aerobic exercise is an effective strategy for moderate weight loss (Thorogood et al., 2011). Thus, this will allow overweight OA patients to reduce stress on their joints and potentially reduce OA symptoms. Aerobic exercise is also known to have positive effects on improving cardiac fitness and blood pressure (Kenney et al., 2015, Dengel et al., 1998), which in turn can decrease the risk of comorbidity and mortality and improve physical function.

Additionally, aerobic exercise showed beneficial effects on pain (ES 0.67, 95% CI 0.39 to 0.94) and function (ES 0.56, 95% CI 0.24 to 0.87) in knee OA patients (Juhl et al., 2014). A systematic review examined the effects of aerobic exercise on knee OA among other types of exercise and found positive outcomes (Fransen et al., 2015). The study identified only four studies (351 participants) examining pain as an outcome and three studies

(317 participants) examined functional outcome of aerobic exercise in knee OA. The review reported overall significant improvement in both outcomes when measured post-treatment, which were sustained for up to 6 months). One of the main studies in this regard is an RCT of 439 adults with knee OA done by Ettinger et al. (1997). The results of this trial showed significant improvements in a number of outcome measures including pain and function. The study was deemed to have a low risk of bias and good overall quality (Fransen et al., 2015).

Aerobic exercise is widely recommended in clinical guidelines (Fernandes et al., 2013). Goh et al. (2018) study has shown that aerobic exercise has the largest ES among all types of exercise on pain outcomes. However, aerobic exercise infrequently has been studied alone in clinical trials. Most studies about hip and knee OA examined the effects of aerobic exercise in conjunction with other types of exercise (Goh, 2018, Fransen et al., 2014). Additionally, the overall evidence for the benefits of aerobic exercise tends to be stronger in knee OA than in hip OA studies due to the scarcity of studies testing aerobic exercise on people with hip OA.

1.2.2.3.3 Other types of exercise

Further types of exercise were studied for OA management. For example, a number of international guidelines recommended the use of flexibility

and range-of-motion (ROM) exercises for OA patients due to the potential benefits shown in the available literature (NICE, 2014, Fernandes et al., 2013). Additionally, mind-body exercises, such as tai chi and combining mindfulness with physical exercises, are showing promising results in OA management (Lauche et al., 2013).

It remains unclear whether exercise should be prescribed in a single, specific type or in a combination of different types to target multiple impairments (Fransen et al., 2015). A recent, systematic review of RCTs examining exercise for lower limb OA suggested that a combination of strengthening, flexibility and aerobic exercise provides most effective outcomes (Uthman et al., 2013).

1.3 Individualisation of exercise

Individualisation of treatment implies that its prescription is personalised and tailored to the patient's characteristics and needs. Individualised exercise (IE) is an evolving concept that aims to optimise the effects of exercise interventions in chronic musculoskeletal management. IE seems to be a promising alternative to the common one-size-fits-all approach, especially when considering the obvious heterogeneity in people with chronic musculoskeletal pain (e.g., chronic low back pain (LBP) and knee OA) (Falla and Hodges, 2017).

Heterogeneity in physical and psychosocial characteristics can significantly affect the intensity of pain sensation, which can affect the outcomes of exercise interventions. For example, patients who suffer from depression and anxiety may not respond to treatment as much as others who are considered psychologically stable. Additionally, people with poor physical condition (e.g., poor fitness or strength) may not cope or adhere to prescribed exercise which affects the results of interventions. Therefore, it is not surprising to see considerable variations in response to standardised exercise interventions in clinical trials, and it is plausible to suggest that prescribing IE can lead to improved outcomes (Falla and Hodges, 2017).

Growing evidence indicates improved outcomes from prescribing IE. Several studies have explored the efficacy of IE in the management of common musculoskeletal conditions such as rheumatoid arthritis (RA) (Metsios et al., 2014, Flint-Wagner et al., 2009), shoulder pain (Eremiev et al., 2020, Kromer et al., 2010) and chronic LBP (Hayden et al., 2005, Falla and Hodges, 2017).

IE has been found to lead to improved outcomes for people with cardiac conditions (Rawstorn et al., 2016, Budts et al., 2013), respiratory conditions (Wanrooij et al., 2014) and mental illness (Lederman et al., 2019).

Overall, IE has been deemed an effective treatment in different healthcare conditions. However, it remains unconfirmed whether IE is superior to non-individualised exercise (NIE) or not. A review published in 2008 looked at studies comparing IE directly to NIE for non-specific LBP and indicated that IE may be better than NIE; however, it could not identify a significant statistical difference (Henchoz and So, 2008).

More recently, a study by Saner et al. (2015) compared an IE consisting of tailored exercise training targeting functional improvement to a general NIE and found no significant difference in functional ability between the intervention groups (both groups showed significant improvement compared to baseline). It is unclear whether this unexpected finding is because of the method of individualisation used in this study or whether there are, in fact, no significant differences between IE and NIE. Therefore, more studies comparing a properly constructed IE versus NIE intervention are warranted.

1.3.1 Individualised exercise in osteoarthritis management

In OA management, the concept of IE is highlighted by NICE and EULAR guidelines (Fernandes et al., 2013, NICE, 2014). These recommendations

agree that individualisation based on patient characteristics is an area that shows significant potential in developing and optimising current interventions. However, the literature underpinning these facts is limited and relies mainly on evidence from a limited number and quality of IE clinical trials, general estimation prognostic factors for OA (e.g., weight, age and gender) and moderators of the effects of exercise intervention (e.g., knee alignment, obesity and comorbidity). (Details about these trials is in the following section)

Clinical trials of IE on people with OA showed positive effects on multiple outcomes in OA. For example, a recent RCT by de Rooij et al. (2017), which provided tailored exercises according to patient comorbidities (mainly cardiac and respiratory conditions), reported significant post-treatment improvements in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for physical function (reduction of 11.6 points = 33%) and numeric rating scale (NRS) for pain (reduction of 1.7 points = 27%).

Furthermore, a study that evaluated the outcomes of IE intervention considered 41 participants with chronic knee pain (Keays et al., 2015). This study utilised a pre/post study design, where participants were assessed before and after receiving the intervention, and there was no control group. The study reported significant improvement in four

functional outcomes: going up stairs, going downstairs, stepping down and during selected activities. A home exercise programme was prescribed at the end of the study and change in outcomes was re-evaluated three years later. The study reported good adherence and sustained improvements in outcomes after three years. The authors indicated that adherence was measured by an exercise diary indicating the number of sessions they completed daily. The reported adherence rate was 60%, meaning that exercises were done twice a day in most patients. However, using self-reported exercise diaries is widely criticised for potential bias. Participants may forget to record their exercise routine or report lying out of embarrassment and report exercises that they did not actually do.

Although clinical trials have examined the individualisation of exercise, the overall level of evidence has not yet been evaluated. Additionally, a consistent issue with studies on IE intervention either in OA or other conditions is that it is not clear whether the improvements achieved are due to the individualisation of the intervention or are merely a response to exercise in general. However, heterogeneity in characteristics of OA patients, in regards to pain intensity, body type, baseline physical abilities, psychosocial wellbeing and presence of comorbidities, makes it logical to claim that a person will respond better to an IE than an NIE, even if no statistical confirmation of this is available yet.

1.3.2 Exercise individualisation factors for osteoarthritis

In order to understand IE for OA, it is important to determine the main individualisation factors for exercise to work better for people with the condition. Understanding ‘what works for whom’ is the core element in the development of an IE intervention for people with OA. Identifying the most relevant individualisation factors can be achieved by reviewing previous clinical trials that have used IE in OA management. This is illustrated in detail as part of the systematic review presented in chapter 3.

A scoping search of the literature revealed a number of trials that have examined the effects of IE in OA patients using a variety of individualisation factors. One study attempted to individualise exercise according to patients’ comorbidities (de Rooij et al., 2017). The simultaneous presence of two or more diseases or medical conditions in people with OA is a common situation (affects 67% of all OA patients) and can seriously affect their ability to perform the required exercises (Swain et al., 2020a). In this study, different mechanisms were used to individualise exercises; patients with cardiac disease received exercise that took into consideration their fitness level and avoided increasing their heart rates. Furthermore, disease-specific education was given to each group of patients.

Another RCT individualised exercise for people based on outcomes of assessments of muscle strength, flexibility and joint range-of-motion (ROM) (Segal et al., 2015). The severity of OA symptoms (e.g., pain intensity and functional ability) and quality of performing the exercises are frequently used measures to personalise an intervention (Thorstensson et al., 2005, Villadsen et al., 2013, Skou et al., 2015). Furthermore, some trials have personalised exercise according to specific patient characteristics, such as gender, BMI and age (Lim et al., 2008, Mikesky et al., 2006b).

A study by Saccomanno et al. (2016b) investigated IE according to the biomechanical influences it would exert on the joint. Different exercise programmes were prescribed according to which knee compartment was more affected by structural changes in OA (medial or lateral tibio-femoral compartment; patello-femoral compartment).

This study was criticised because there were minimal differences between the individualised exercise programmes prescribed to each group. The prescription included isometric strengthening of the quadriceps for all the groups, while the difference lay in prescribing the strengthening of tensor fascia-lata and hip adductor medial flexors to the medial tibiofemoral compartment group and lateral tibiofemoral compartment group, respectively. Therefore, due to this overlap in exercise programmes, it is

difficult to determine whether the improvement was related to the individualisation of the intervention or the strengthening of the quads that all groups received.

The current RCT literature shows significant variations in regard to the basis of individualisation methods. However, a recent systematic review provided significant input in this regard. The review investigated the moderators of the effects of therapeutic exercise for people with knee and hip OA (Quicke et al., 2020). The study considered 14 RCTs (13 for knee OA and one for hip OA) involving a total of 2946 participants. It searched exclusively for studies that investigated individualisation factors of exercise for people with OA and identified a number of factors, including varus knee malalignment, obesity, cardiac problems, varus thrust, knee laxity, knee instability and upper leg strength. These factors were considered as potential moderators of effects of therapeutic exercise. However, the study revealed that the evidence is still limited due to limitations in sub-group analyses and the small number of studies.

Furthermore, an ongoing study by Holden et al. (2017) is expected to substantially develop understanding of the best ways to indivdualise exercise for people with OA. The full study has not been published yet, but according to the protocol published in 2017, the authors are investigating the individual participant data (IPD) of people with OA involved in clinical

trials of exercise therapy. The study aims to identify potential factors to help in optimally subgrouping exercise programmes for people with knee OA. The objectives of the study include multiple important items, among them three which are relevant to IE:

1. To determine exercise characteristics that could improve overall effects, such as type of exercise, intensity and duration.
2. To identify individual-level characteristics of people with knee and hip OA that could moderate the effects of therapeutic exercise on pain and function.
3. To identify the relationship between individual characteristics and exercise characteristics that could lead to improved outcomes.

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Some intermediate results from this study were published in a conference abstract (Holden et al., 2019). The results showed that some mediating factors are linked to effects of exercise in managing people with knee and hip OA. For example, the study found that those with greater motivation to exercise, greater self-efficacy and better outcome expectations are likely to have better improvements in pain and function from exercise interventions. While those who suffer from depression and anxiety are likely to have minimal improvement with exercise. These results indicate that psychological factors are important mediating factor for exercise interventions .

Additionally, lower level of baseline physical activity is often linked with greater improvement in response to exercise while those with good level of baseline physical activity benefit less from the intervention. This mean that individualisation is important in order to identify which type of exercise does the patient really need. Because if physical activity was prescribed to an active person, it probably will not lead to significant improvement and vice versa.

It is hoped that analysing previous trials in depth and detail will answer many significant queries about how to optimally individualise exercise for people with OA. However, such large studies may face multiple challenges (e.g., inability to access IPD for some studies) and to date, many of these queries remain unanswered.

1.3.3 Behavioural change

Exercise therapy, by nature, requires behavioural change as it entails patients to make conscious decisions to engage in new activities on an ongoing basis. Therefore, it is important to understand the theoretical basis of behavioural change and how individualisation of exercise can help promote positive changes in patients' behaviour (Room et al., 2017). This

should be done in relation to relevant theoretical frameworks, which will help provide firm grounds for developing interventions.

A systematic review by Ferrier et al. (2011) examined the effects of behavioural change interventions used in cardiac rehabilitation. The review included 24 studies with a total sample of 2,546 patients and revealed that there are significant improvement in adherence with physical activity interventions and using behavioural change strategies (such as education, general encouragement and goal setting) compared to physical activity interventions alone. Another and more recent review by Room et al. (2017) concerns the use of behavioural techniques to improve adherence in older people. In this review, out of the 11 studies included, only 4 studies were found to have used recognised behavioural theories or frameworks for support, specifically social learning theory, socioemotional selectivity theory, cognitive behavioural therapy intervention theory and Bandura's self-efficacy theory. Both reviews criticised the included studies for failing to use theoretical backgrounds to underpin the behavioural change techniques used alongside the interventions.

1.3.3.1 ***Self-efficacy theory***

Exercise and physical activity researchers usually adopt theories and models of behavioural change from pioneers in social and health

psychology (Sutton, 2004). Among these theories is Bandura's theory of self-efficacy, which is a commonly used, competence-based theory on changing behaviours in patients with chronic conditions, including OA (Biddle et al., 2007).

Self-efficacy theory was in developed in 1986 by social cognitive psychologist scientist Albert Bandura. This theory is mainly concerned with people's beliefs of their own abilities to perform a specific task or course of action (e.g. exercise)(Bandura, 1986). In exercise psychology, the lack of self-belief can have two forms: some people may have low confidence in their own capabilities to execute the action of exercise (self-efficacy), while others may have problems with outcome expectations (e.g. whether the exercise will produce a specific result or not) (Biddle et al., 2007).

The theory suggest that self-efficacy in important factor in initiation and maintenance/adhrence of any exercise programme. In order to optimise adherence with exercise, Ewart et al. (1992) believes that exercise should first be prescribed in gradually increasing doses. Second, exercise should be provided in an environment where subjects are surrounded by others in a similar state of performing exercises, which can make subjects consciously or unconsciously model and imitate these other people. Third, care providers should offer support, reassurance and motivation. Finally, the environment surrounding the exercise prescription should be relaxed

and considerate of subjects' psychological states. These strategies represents the four main pillars of Bandura's theory in practice: performance, modelling, persuasion and emotional and psychological states (Figure 1.4) (Bandura et al., 1999).

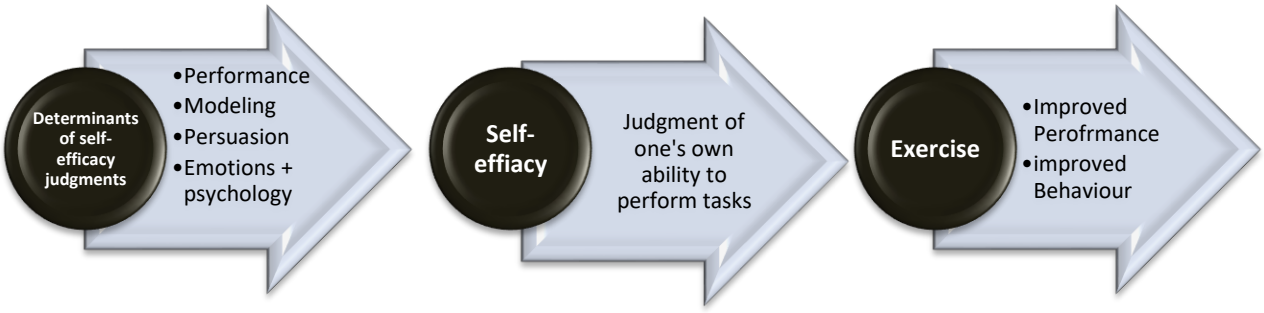


Figure 1-4. Self-efficacy theory diagram

A considerable body of evidence has investigated the usefulness of this theory in exercise prescription. For example, a survey done by Hofstetter et al. (1991) examined aerobic exercise (walking) perceptions in a weight loss programme for a large sample of adult population (2,053 participants). The study showed that self-efficacy levels were linked to participation in and maintenance of the walking programme. However, it was not clear how self-efficacy was measured.

Edward McAauley investigated self-efficacy and exercise in multiple trials (McAuley, 1992, Mcauley and Courneya, 1993, McAuley, 1998, McAuley et al., 2001). The most important messages from these studies can be

summarised in four main points: (1) self-efficacy can improve with interventions, (2) self-efficacy can predict levels of participation in exercise, (3) inactivity can adversely affect personal self-efficacy judgments and (4) there is a clear association between self-efficacy and positive emotions in exercise (Biddle et al., 2007).

1.3.3.2 *Self-efficacy in osteoarthritis management*

Considering self-efficacy as part of exercise individualisation is specifically important for people with OA due to the association between level of self-efficacy and severity of OA symptoms (Lawrence et al., 1998). Perceived reduction of physical ability and poor pain coping strategies that come with OA symptoms may lead to loss of confidence and perception of helplessness (Allegrante and Marks, 2003). Thus, low self-efficacy may lead to further inactivity, leading to decreased physical ability, in a vicious cycle of events. Regardless of an individual's belief in the benefits of exercise, people's engagement with exercise might diminish substantially when there are low self-efficacy levels (Gecht et al., 1996).

Evidence from reviews of the literature indicates that level of self-efficacy is a significant factor in mediating management outcomes in people with OA (Allegrante and Marks, 2003). Furthermore, recent observational studies have supported this claim. A large study that involved 3266 participants with hip or knee OA investigated the association between

baseline self-efficacy level and change of pain and physical activity overtime (Degerstedt et al., 2020). The study revealed that high self-efficacy positively influenced pain outcomes and engagement with physical activity in people with OA. The authors indicated that these findings highlight the importance of exploring and strengthening self-efficacy both in clinical practice and when developing interventions for people with OA (Degerstedt et al., 2020).

However, it should be noted that assessing and mediating self-efficacy levels in people with OA is challenging. Improving self-efficacy first requires the current level of self-efficacy to be determined and the identification of areas that need improving. Therefore, a specific instrument has been devised for this purpose. The Arthritis Self-Efficacy Scale is a tool designed specifically to assess levels of self-efficacy in people with arthritis (Lorig et al., 1989).

Despite some criticism of its methodological quality (Garratt et al., 2014), this tool has been widely used due to its acceptable reliability and validity (Garratt et al., 2014, Barlow et al., 1997). It should be noted that the scale may show natural differences between people, but there is no established cut-off point to differentiate between low and high efficacy (Brand et al., 2013).

1.4 Study rationale

Although exercise has been shown to be an effective intervention for OA knee pain and function, it is not effective for everyone. Current literature shows that there is a need to maximize the effects of this intervention (Fernandes et al., 2013, Bennell et al., 2014). Even in well-conducted trials that demonstrate significant improvements in pain outcomes and function scores, clinically significant benefits were only found in 40% of patients (Hay et al., 2006).

Poor clinical response and a tendency not to maintain improvements with exercise are attributed to a variety of factors. For example, uncertainty exists regarding specific exercise characteristics such as dose (number of exercise sessions in total), frequency (how many sessions per month or week), duration and intensity (amount of muscular exertion) (Bennell et al., 2014, Fernandes et al., 2013, Juhl et al., 2014), although these characteristics are known to have a potential impact on the outcomes of an intervention (Lundebjerg, 2001). Furthermore, a major challenge for those involved in prescribing therapeutic exercise interventions is lack of engagement or adherence. Persuading patients to regularly perform therapeutic exercises is challenging, especially with frail older adults (Bundon et al., 2011).

Campbell et al. (2001) explored the issue of engagement and adherence with exercise interventions in physiotherapy. They interviewed 20 patients attending exercise-based physiotherapy sessions and summarised the findings of this qualitative study in what they termed a 'model of continued compliance' (Figure 1-5). This model shows the relationship between the perceived effectiveness of an intervention, the condition and the motivation (the logic that explains the reasons for compliance or non-compliance).

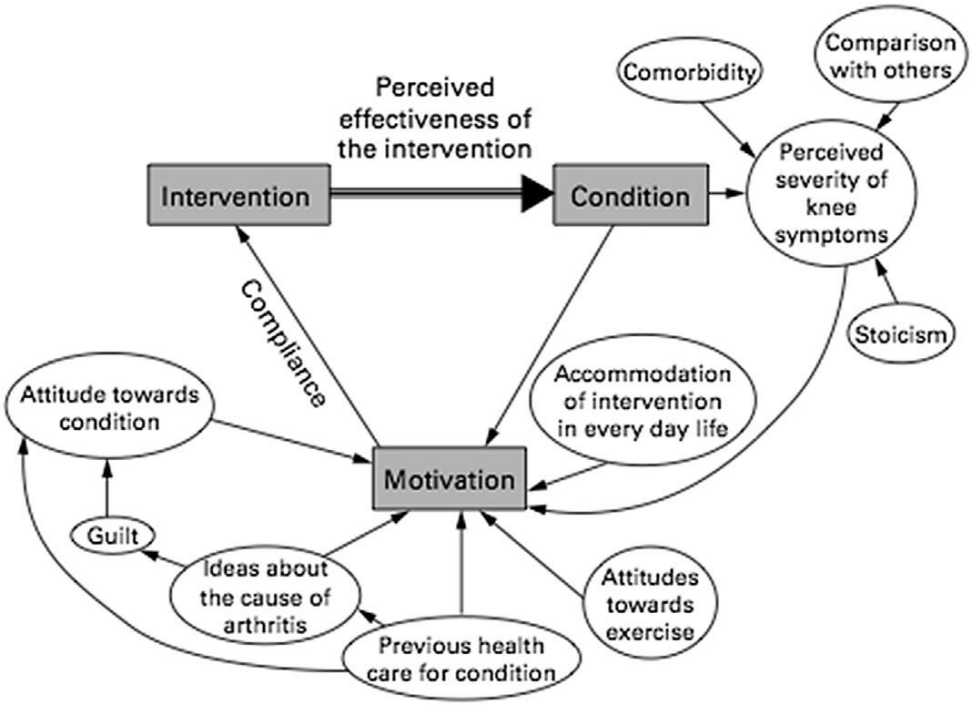


Figure 1-5. Factors affects compliance with exercise (Campbell et al., 2001)

In brief, the model of continued compliance argues that for a person to comply with therapeutic intervention, continues the circle of positive perceptions regarding intervention, condition and motivation need to be

sustained. If the person perceives exercise as an effective intervention, understands the condition's nature (e.g., OA), and could maintain a good level of motivation despite the surrounding factors, they are more likely to comply and adhere to the prescribed exercise.

1.4.1 Adherence to exercise

Adherence is critical in making exercise a successful intervention (i.e. exercise is only effective if it is performed) (Bennell et al., 2014). An 18-month clinical trial of 439 participants by Ettinger et al. (1997) showed a significant dose-response association between exercise effects and adherence. Conversely, it has been demonstrated that a lack of adherence adversely affects the outcomes of exercise interventions (e.g. pain, functional ability and physical performance) (Pisters et al., 2010, Van Gool et al., 2005). In exercise generally and in OA specifically, people tend to have high adherence to exercises in the initial stages, but this decreases as time passes (Campbell et al., 2001, Goh et al., 2019a). In order to solve this issue, it is argued that exercise interventions should be patient-centred, individualised and flexible to suit a variety of barriers to adherence in different individuals (Bennell et al., 2014).

Current literature shows that the lack of adherence to exercise and other home-based physiotherapy interventions is largely related to behavioural and social factors. This is attributed to a number of factors, including

decreased baseline levels of fitness, low self-efficacy, anxiety, perceived barriers to exercise and pain induced during exercise (Jack et al., 2010). This indicates the significance of theory-based behavioural change strategies (Room et al., 2017) and making the intervention more patient-centred, individualised and flexible to suit a variability of barriers to adherence in different individuals (Bennell et al., 2014).

Additionally, adherence to exercise is also affected by lack appropriate information from health practitioners, not addressing illness perceptions appropriately, and making exercise a “treatment” rather than incorporating it as a lifestyle adaptation.

1.4.2 Why individualisation of exercise is needed

By individualising exercise interventions, researchers seek to maximise the benefits of these interventions. This is thought to be achieved by first tailoring an intervention to an individual’s characteristics (e.g., OA severity, pain intensity, muscle performance, and age). Secondly, it is important to individualise exercise to fit exercise programmes into an individual’s lifestyle according to their preferences and needs. This should be done following appropriate behavioural change facilitators (e.g., improving self-efficacy and motivation). This potentially can improve effectiveness, adherence and adherence to exercise intervention.

1.4.3 Research aim and objectives

Although individualisation of exercise is recommended by international guidelines (Fernandes et al., 2013), there are several questions which are, as yet, unanswered.

Does IE lead to better outcomes for people with OA compared to non-individualised exercise (NIE), in terms of overall effect size and the proportion of people who achieve clinically meaningful improvements?

Is exercise adherence better in individual exercise interventions? How should exercise be best individualised for people with OA?

The current study will attempt to answer some of these questions and improve the current understanding of IE intervention. This will be achieved through the following aim and objectives.

Aim:

This study aims to develop an optimal, IE package for people with hip and knee OA.

Objectives:

1. To evaluate the current evidence for IE interventions of hip and knee OA using a systematic review.
2. To generate a consensus of opinion from a panel of healthcare professionals and patients as to the optimal strategies for individualising exercise interventions for OA using Delphi consensus methodology.
3. Develop a protocol for an individualised exercise programme for knee OA.
4. To test the acceptability of delivering an optimal, IE intervention for patients with knee OA.

Chapter 2. Methodology

2.1 Medical research council framework for intervention development

Complex interventions such as exercise can be defined as any interventions that have multiple interacting components. Therefore, complexity can have several dimensions, such as flexibility in intervention delivery, behaviours of therapists or patients and outcome variability (Skivington et al., 2021b). However, in order to provide the best evidence-based practices, interventions should be developed systematically and grounded in relevant theories.

The Medical Research Council (MRC) provides a clear and well-structured framework for developing and evaluating complex (Skivington et al., 2021b). This framework involves four main stages: development, feasibility or piloting, evaluation and implementation (Figure 2-1). However, the focus of this PhD project is on the development phase of this sequence and feasibility testing.

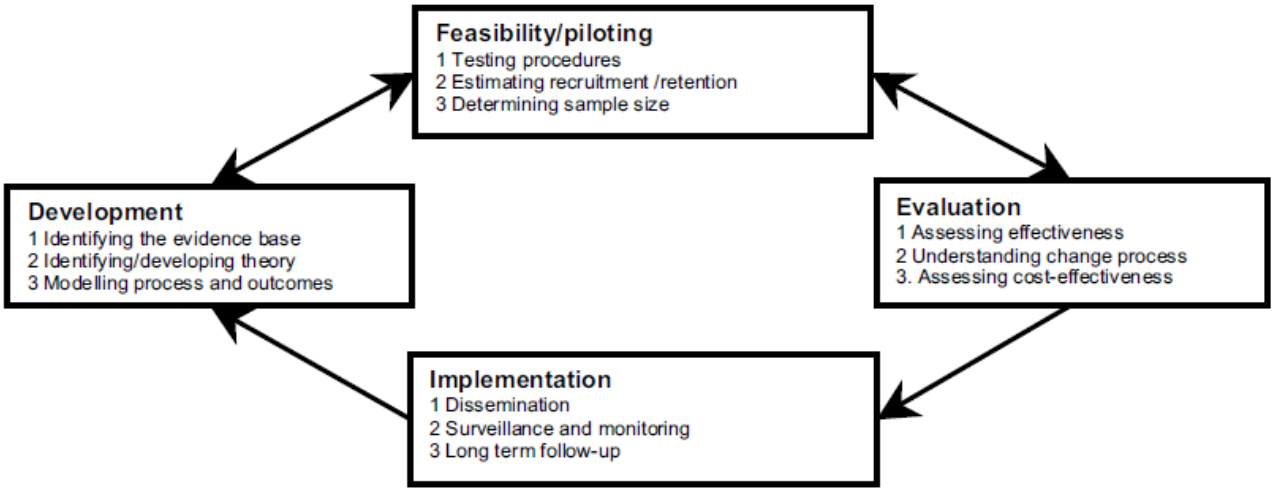


Figure 2-1. Developing and evaluating complex interventions (Craig et al., 2013)

2.2 Intervention development process

The MRC framework recommends the following 3 stages to develop interventions prior to testing them in substantial evaluation trials:

1) ***Identifying evidence*:** This stage should typically involve a comprehensive method to search and evaluate the existing literature on the topic of interest. In this study, a systematic review will be conducted on IE interventions used to treat hip and knee OA.
2) ***Identifying or developing an appropriate theory:*** In this stage, the researcher should provide a rational and logical concept for the intervention being developed. This can include a rationale on how the intervention might work, what factors affect the outcomes of the

intervention, and how this individualised intervention can improve effectiveness and adherence compared to standardised intervention. In this study, the rationale for developing the intervention was constructed from a variety of resources, including evidence collected from the systematic review of current literature on exercise intervention, experts' and patients' opinions obtained by conducting a Delphi study and stakeholder's meetings, and theories from wider literature.

3) ***Modelling*****:** This stage should provide researchers with a clear picture of the elements the intervention will be tested. Modelling typically involves using gathering evidence and knowledge to develop a plan for the intervention then evaluate its weaknesses and strengths, which can lead to necessary amendments before testing (e.g. acceptability, feasibility, etc.). The intervention plan can then be amended and enhanced again according to testing results as intervention development is an ongoing process (Craig et al., 2013). For this project, modelling will involve utilising findings of the SR and experts' opinions combined with core knowledge and experience of the study team to construct an optimised IE intervention and test its acceptability.

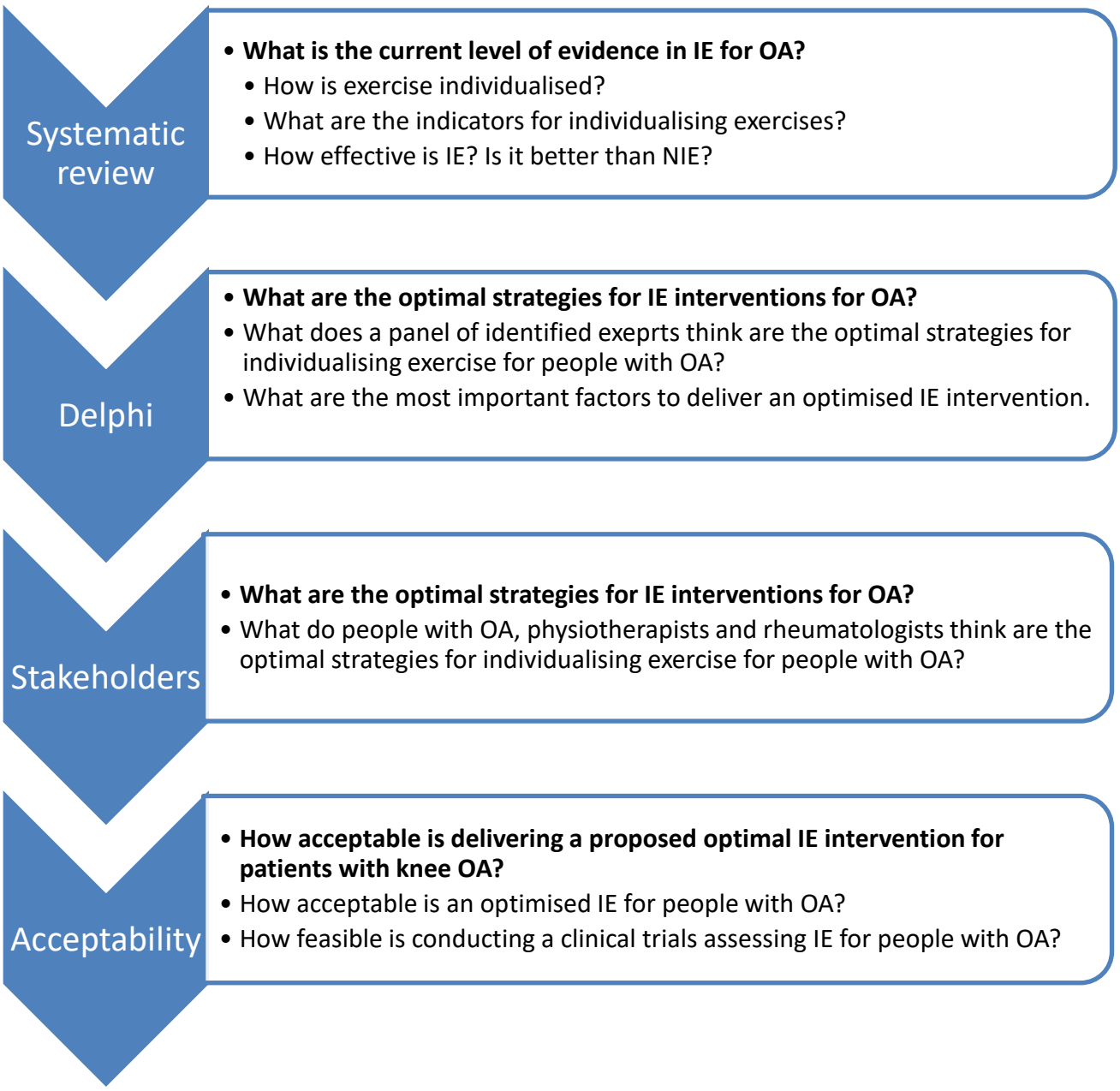


Figure 2-2. Summary of the studies of this PhD project

This PhD project involved using four research methodologies (Figure 2-2).

Brief background of each methodology is described below.

2.3 Systematic review

Systematic reviews, as defined by Cook et al (1997, p. 377), are ‘scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their subjects. Thus, a systematic review is known to be a secondary source of evidence resulting from comparisons and evaluations of evidence from primary resources (Cook et al, 1997). The systematic review is at the top of the hierarchy of evidence in research for effective questions and has been referred to as one of the most reliable methods for defining existing evidence and comparing clinical trials, which helps clinicians identify the best available evidence in the field of practice (Jones and Evans, 2000).

Although this method is popular and efficient, it still has some disadvantages (Askie and Offringa, 2015). Conducting a thorough systematic review, properly performing all the steps, is a costly and time-consuming process. In some instances, it takes more than one full-time researcher over a prolonged period of time. Additionally, conducting an extensive search may be subject to human error. Researchers may miss out some important studies while screening, or software errors may lead to related studies being missed. The quality of the included studies may also be a limitation on the overall results of systematic reviews. It is possible that many of the included trials have a high risk of bias or reporting limitations (Askie and Offringa, 2015).

2.3.1 Meta-analysis

Meta-analysis can be carried out on quantitative data gathered in the process of systematically reviewing the literature. In conventional meta-analysis (CMA), data is combined in a statistical way, which enables researchers to compare and critically appraise the evidence (Cook et al, 1997). Therefore, the higher the quality of the trials or studies included (e.g. RCTs), the better the quality and accuracy of the pooled results (Cook et al, 1997). However, meta-analysis is not always indicated. Homogeneity of samples, interventions and outcomes of included studies is key in deciding whether an meta-analysis is appropriate or not (Haidich, 2010).

Additionally, a new, advanced multiple pairwise technique of meta-analysis called network meta-analysis (NMA) has emerged. NMA differs from CMA in that it enables researchers to compare the pooled effect size of multiple interventions using a common comparator (Dias and Caldwell, 2019). For the majority of health conditions, there are more than two interventions of interest. Therefore, a complex method of analysis is needed to inform the decision-making process.

2.4 Delphi

Delphi methodology is a consensus-based evidence technique that has been used widely used in healthcare research and guidelines and, more specifically, in research concerned with interventions (RCPL, 2015). The name Delphi is a reference to an ancient Greek temple called Oracle of Delphi. It is claimed that this temple was of anonymous voting system to reach a mutual agreement on a specific matter (Dalkey and Helmer, 1962). This method was developed during the cold war and was used as a research method to evaluate the impact of technology on warfare (Custer et al., 1999).

Delphi exercise is an iterative process that involves a systematic progression of repeated rounds of voting to reach consensus for a defined clinical problem. This method is recommended for healthcare settings and is an effective process in determining experts' consensus where there is a lack of evidence and where opinion is essential (Meshkat et al., 2014, Fernandes et al., 2013, Murphy et al., 1998). Anonymity is one of main advantages of Delphi studies. Anonymity may encourages honesty and creativity while reducing the risk of having group dynamics affecting participants' opinions (Donohoe et al., 2012).

Delphi exercise alongside the stakeholders meeting presents a valuable input to the process of intervention development. These studies can be an

alternative source of evidence to identify the best ways to individualise exercise. They also help identify new ideas and methods to be considered from participants' clinical and academic experience. Such ideas cannot be identified from reviewing published trials, however, it can be insightful and effective in treating people with OA.

However, there are some limitations to Delphi studies. Agreed standards and guidance are inadequate to identify experts/participants and interpret results and define consensus (Fink-Hafner et al., 2019). Delphi studies are time-consuming not only for researchers but also for participants, which usually leads to a high drop-out rate. Additionally, drop-out may happen as a result of distraction between rounds or frustration with the iterative process (Donohoe et al., 2012). Furthermore, anonymity is one of the main features of Delphi studies, but it may introduce a feeling of less ownership of ideas and can be a limitation on the results (Fink-Hafner et al., 2019).

2.5 Stakeholders' meeting

Stakeholders are universally known as individuals, an organisation or a community that have an interest in specific processes and/or outcomes of a policy endeavour, project or research (Deverka et al., 2012). Engaging stakeholders in the intervention development process helps minimise the gap between researchers, clinicians, patients, and policy makers (Boaz et

al., 2018, Forsythe et al., 2018). Having stakeholders' perspectives on board helps to guide the development of research ideas and implementation of study results into clinical practice. Studies that use stakeholders' input are often seen as more feasible and trustworthy, and are highly appreciated by the public (Bowen et al., 2017, Martinez et al., 2019, Forsythe et al., 2016).

However, there are some challenges to carrying out a stakeholders' meeting. Organising such meetings might face difficulties in relation to co-ordinating times and venues for attendees (O'Haire et al., 2011b). Additionally, meeting face-to-face in a group context may make some individuals reticent to express their opinions. Group dynamics may affect the flow of conversation and distract the meeting from focusing on the most important topics. Coordination and prioritising the topics of discussion are important aspects to obtain information within a reasonable meeting duration (O'Haire et al., 2011b).

In the context of developing healthcare interventions, stakeholders' involvement is considered a core element of the development process. Stakeholders' input is essential in defining research questions, initial intervention development stages and overcoming hurdles to implementation and re-evaluation (Skivington et al., 2021b). However, there may be potential conflicts of interest between researchers and

stakeholders. Tensions can exist between different individuals, such as intervention developers and funding structures (Turner et al., 2019). For example, some stakeholders' opinions may prioritise cost-effectiveness over the costly beneficial treatment plan. Although their ideas might be sensible, it is still essential to understand the priorities and background of the stakeholders involved and make sense of their input within the overall aims of the intervention development process.

2.5.1 Public Patient Involvement:

Involving the public in medical research infers that they take part in the decision-making of how research is designed, conducted, and disseminated. In Public Patient Involvement (PPI), the research is done by the public rather than on or to them. In other words, the public participates in the researchers' role, not only being participants in trials. Involving the public and the patients in research has multiple benefits, such as making the research relevant, understandable and acceptable to participants (NHS, 2022).

Involving the public can be done in different stages of research. The public can take part in macro-level research development (e.g., identifying the topic and reviewing evidence) and Meso-level (e.g., recommendations) (e.g., recommendations) (Boivin et al., 2010).

According to Raine et. (2016), The public's early involvement in the development of interventions can lead to a meaningful impact on practice. This involvement can be done by communicating information to the public/patients, consulting the public, and exchanging information between the public and the other stakeholders (Rowe and Frewer, 2005).

2.6 Acceptability

In healthcare, testing acceptability of interventions is becoming a key consideration when it comes to designing, implementing, and evaluating an intervention (Sekhon et al., 2017). Healthcare interventions such as exercise are complex and comprise multiple interacting components. Therefore, intervention developers face many challenges in designing effective complex interventions that ensure achieving optimised outcomes.

Acceptability studies are needed to understand the elements of a successful delivery of an intervention from the perspectives of recipients' (e.g. patients) and deliverers' (e.g. healthcare professional) (Diepeveen et al., 2013). For example, factors such as content of intervention, care quality, and context are factors that can have a significant implication on recipients' acceptability. Thus, if delivery of a specific intervention has obtained high acceptability, the recipient is more likely to adhere to it and benefit from its projected outcomes (Fisher et al., 2006, Hommel et al., 2013). High acceptability from the deliverer's point of view means that the

intervention delivery is delivered as intended by the intervention designer(s) and therefore can be tested in large scale trials to assess its effectiveness (Borrelli et al., 2005, Proctor et al., 2009). This is also known as fidelity (to what extent the intervention was delivered as planned) which is a critical aspect of interventions' delivery.

Furthermore, assessing the acceptability of any complex intervention (e.g., exercise) can be challenging for multiple reasons (Sekhon et al., 2017). For example, in typical acceptability studies, the number of participants is relatively small. Therefore, they may not reflect the actual acceptability of an intervention. The delivery of complex interventions is affected by multiple factors; therefore, it needs to be tested on a large number of participants. Additionally, in many situations the level of retention and acceptability of an intervention during acceptability studies is different to that in the actual RCTs. This shows that the robustness of acceptability studies needs to improve in order for them to accurately predict the acceptability of interventions in large trials (Sekhon et al., 2017).

Chapter 3. Efficacy of individualised exercise in osteoarthritis.

3.1 Introduction

This chapter presents a systematic review, CMA and NMA of RCTs to evaluate the evidence for IE interventions in people with hip or knee OA and to compare it with evidence for NIE. The evidence gained from the literature for the IE and NIE review was first summarised using a CMA. This was followed by an NMA that directly compared the efficacy of IE versus NIE in RCTs. This review was registered with the international prospective register of systematic reviews (PROSPERO) on 11-05-2018.

3.2 Aim and objectives

The aim of this systematic review was to determine the efficacy of individualised exercise intervention for people with hip or knee OA.

Objectives:

1. To systematically search for RCTs that report the use of an individualised exercise intervention in hip and/or knee OA.
2. To evaluate the quality of the existing evidence.
3. To identify the ways in which exercise is individualised.
4. To evaluate the quality of reporting of IE interventions

5. To perform a CMA in order to estimate the size of the effect of IE interventions and to compare this with NIE interventions for pain, self-function, functional performance and quality of life (QoL).
6. To compare the effects of IE versus NIE using an NMA.

3.3 Methods

3.3.1 Search strategy

This review involved two independent searches one for IE interventions and another for NIE interventions using the following databases:

- Medical Literature Analysis and Retrieval System Online (MEDLINE).
- Cumulative Index of Nursing and Allied Health Literature (CINHAL).
- The Allied and Complementary Medicine Database (AMED).
- Psychological Information Medical (PsycINFO).
- Excerpta Medica Database (EMBASE).

No language restrictions were applied. The search results from each database were exported to EndNote software, where duplicates were removed prior to the screening process. The full search strategy for IE in the MEDLINE database can be found in Appendices

Appendix 1: Search strategy).

A previous search for all exercise interventions for hip and knee OA conducted by (Goh et al., 2019b) was used to validate the search findings from the strategy above and to provide a comparator group of NIE. A further search for any exercise was updated and new studies for IE and NIE were added.

3.3.1.1 ***Search date***

Searches of IE and NIE studies were applied from inception until December 2017. Both searches were updated on 5th April 2020.

3.3.1.2 ***Study Selection***

The screening process was conducted in three stages. Firstly, the titles of the search results were screened for relevant studies, secondly, the abstracts of the relevant papers were screened, and thirdly, the full texts of papers were scrutinised to ensure their relevance to the focus of the review. Reference lists of the included studies were hand searched to identify any additional relevant studies. The work for this review was done by four reviewers; Khalid Yaseen (KY), Siew Li Goh (SG), Burka Kundakci (BK) and Ayah Ismail (AI).

The screening process for IE studies was completed by KY and validated by BK. This process involved screening the titles, abstracts, and full text of all potential IE studies. The initial search of the titles and abstracts of all types of exercise for hip and knee OA (until 2017) was conducted by Goh et al. (2019). The full-text screening for this review's eligibility for NIE inclusion was completed by KY. The search update for both IE and NIE was completed by KY. The specific involvement of each reviewer is detailed in Appendix 2: Reviewer's involvement.

3.3.2 Eligibility

3.3.2.1 *Types of studies*

Only full randomised controlled trials (RCTs) were included in the review. Protocols, pilot RCTs and all other study designs were excluded.

3.3.2.2 *Participants*

The review included studies of participants with symptomatic knee or hip OA confirmed by either clinical assessment, e.g. ACR criteria (Altman et al., 1986), or radiographic assessment for structural OA (e.g. using KL criteria) (Altman et al., 1986, Kellgren and Lawrence, 1957). Studies involving people who had recently undergone total joint replacement, who had OA and rheumatoid arthritis in a mixed sample, or who had undiagnosed general joint pain were excluded from the review.

3.3.2.3 ***Interventions***

IE is any form of exercise that is modified according to specific participant characteristics (e.g., pain severity, presence of comorbidities and BMI). Only studies that reported the individualisation of exercise regimes, using terms such as “individualised exercise”, “personalised exercise intervention”, “stratified exercise intervention” and “tailored exercise programmes”, were included.

Studies in which subgroup analysis was carried out based on personal characteristics were included in the search but not included in the meta-analysis. Such subgroup analyses may help to identify whether such characteristics can be used to individualise exercise intervention.

3.3.2.4 ***Comparators***

Any comparators that did not involve IE were utilised in the review, including NIE, usual care, observation only, placebo, and any other intervention. This enabled the identification of all studies involving IE in any context. For meta-analysis, only studies that compared IE or NIE to usual care were included.

For the NIE search, only studies that compared exercise to usual care were included.

3.3.2.5 ***Outcome***

Pain was the primary outcome measure. Secondary outcomes were physical function, QoL and objective physical performance measures.

3.3.3 Data extraction

Data extraction was performed systematically on all included studies using a data extraction form (Appendix 3: Data extraction tool (Example)). This form included general study information (e. g. title, country source of fund, etc.), study design details, the numbers and characteristics of participants allocated to intervention and comparator groups (e. g. number, age and gender). Outcome data, including baseline outcome scores, and results for all study time-points were extracted. Intervention details for both treatment and control arms and a detailed description of exercise and individualisation methods were extracted. Data from all the individual extraction forms were exported into a single database developed using Microsoft Access.

Primary and secondary outcomes related to the purpose of the review were extracted at baseline, eight weeks (or most proximate), and at end-

point. Intention to treat data were collected where reported. No data were extracted from figures unless numerically stated.

3.3.3.1 *Validation of data extraction*

A second reviewer (BK) independently extracted the data from a randomly-chosen selection amounting to 20% of the included studies. Points of disagreement were resolved through discussion with the second reviewer and, if needed, in consultation with the primary supervisor (MH). Data were amended accordingly following this validation process.

3.3.3.2 *Missing data*

SD was a frequently missing value in some of the included studies. If possible, it was calculated from other data such as SE and 95%CI provided in trials (Table 3-1). There was the intention to contact authors for SD if it was not possible to estimate from the data reported in trials. However, this was not necessary since all required data could be determined from the information presented.

Table 3-1. SD calculation formulae

Calculations	Notes
SD from SE and CI • $SD = SE \times \sqrt{N}$ • $SD = \frac{(UpCI - LwCI) \times \sqrt{N}}{3.92}$ SD from median • $SD \cong \frac{1}{12}\left(\frac{(a-2m+b)^2}{4} + (b-a)^2\right)$ SD from interquartile range • $SD \cong \frac{q_3 - q_1}{1.35}$ SD of the change from baseline • $SD = \sqrt{SD_{baseline}^2 + SD_{final}^2 - \left(2 \times r \times SD_{baseline} \times SD_{final}\right)}$ Mean from median • $x = \frac{a+2m+b}{4}$	SD = standard deviation SE = standard error CI = confidence interval N = sample size UpCI = upper confidence interval LwCI = lower confidence interval a = minimum value b = maximum value m = median q_3 = third quartile q_1 = first quartile x = mean

3.3.4 Quality appraisal of studies

Study quality and risk of bias of IE studies were assessed independently by two researchers (KY, BK), using the Cochrane Collaboration's risk of bias assessment tool (Appendix 4: Quality appraisal tool) (Higgins et al., 2011). Additionally, for studies identified in the search update, quality appraisal was assessed by KY and validated by a third reviewer (AI). Disagreements were resolved by discussion and, if necessary, through consultation with the primary supervisor (MH). The assessment tool is composed of nine questions that assess six domains: selection bias; performance bias; detection bias; attrition bias; reporting bias; and other bias.

3.3.5 Intervention description assessment

An evaluation of the quality of the description of the intervention of IE studies in the included trials was conducted using the Template for Intervention Description and Replication (TIDieR) (Yamato et al., 2016). This tool is a 12-item checklist commonly used to assess the completeness of the intervention description (Table 3-2). Providing adequate information about interventions is fundamental for the development of evidence and for informing clinical practice (Conn, 2012) (See full check list form in Appendix 5: TIDeiR checklist). Item number 9 (tailoring) was used to define the individualisation method used in the

study. The evaluation of the intervention description was undertaken by KY and a validation of 20% of the included studies was completed by a third reviewer (AI).

Table 3-2. Summary of Template for Intervention Description and Replication (TIDieR) checklist

Item	Description
1. Brief name	A brief name or phrase to describe the intervention is provided
2. Why	A rationale or theory of the essential elements of the intervention is provided
3. What	A description of any physical or informational materials used in the intervention is provided
4. Procedures	A description of procedures and activities used in the intervention is provided
5. Who provided	A description of the intervention provider's expertise, background and any specific training is provided.
6. How	A description of the mode of delivery is provided (e.g., supervised or internet-based)
7. Where	A description of the location where the intervention took place is provided
8. When and how much	Details of number of sessions, frequency, intensity, and duration of the intervention is provided
9. Tailoring	Details about whether the intervention is individualised or not and description of the individualisation process (e.g., what, why, and how).
10. Modifications	Information about the changes made to the intervention during the course of the study.
11. Planned adherence assessment	Details about whether adherence and fidelity assessment were planned to take place.
12. Actual adherence assessment	Details about whether adherence and fidelity assessment were actually to take place.

3.3.6 Assessment for publication bias

Assessment of funnel plot symmetry was performed visually. This funnel plot uses the results of included studies to present an overall distribution of data. Asymmetrical distribution of data is suggestive of potential publication bias (Higgins and Green, 2011). Egger's test is usually used to assess the possibility of a small study effect, however, it is recommended only if the number of studies included in the analysis is 10 or more and the number of included studies is insufficient to rationalise statistical evaluation of a small study effect (Sterne et al., 2011).

3.3.7 Data management

3.3.7.1 *Database establishment*

Data extracted from the studies included in the review were stored in a database created using Microsoft Access software. The data were organised within the database using the following tables:

1. Main table
2. Study characteristics
3. Participant information
4. Study groups
5. Exercise characteristics
6. Quality assessment
7. Pain results

8. Function results
9. Performance results
10. Quality of life results

These tables were linked using study identification numbers, with one allocated to each study, which facilitated the extraction of data through queries for analysis purposes.

3.3.7.2 *Data entry and calculations*

Data were transferred manually from the extraction forms into the database and were checked for any missing variables. Furthermore, calculations required for analysis purposes, such as the change in mean from baseline to end-point, were completed using Excel software. The results of these calculations were also entered into the database.

3.3.8 Data analysis

Two statistical methods of evidence synthesis were used in this study: conventional meta-analysis (CMA) and network meta-analysis (NMA).

3.3.9 Conventional meta-analysis

CMA is commonly used to compare different interventions where there is a direct comparison or estimate of the effect of a specific intervention versus control. The main aim of the CMA is to calculate the overall efficacy of IE versus usual care and NIE versus usual care in all included studies. ES for continuous data were presented as standardised mean difference (SMD).

For each individual trial, the SMD was calculated by taking the mean difference between intervention and control in terms of change from baseline scores, divided by the pooled SD of the change scores between the two groups. The pooling of the SMDs from the studies was completed using the random effects model in Software for Statistics and Data Science (StataSE). By applying the CMA commands, the software calculated individual SMDs and pooled SMD with 95% CI. A forest plot for each outcome was automatically produced. The forest plot provides details of each included study, pooled results, and level of heterogeneity.

3.3.9.1 *Assessment of heterogeneity*

To quantify the influence of the heterogeneity of results on the pooled estimates, the I^2 statistical test was used. The magnitude of heterogeneity reflected in the I^2 value is interpreted as follows (Higgins and Green, 2011):

- 0%-40% No significant heterogeneity
- 30%-60% Moderate heterogeneity
- 50%-90% Substantial heterogeneity
- 75%-100% Considerable heterogeneity

3.3.10 Network meta-analysis

The second part of the data synthesis process was an NMA. An NMA enables researchers to estimate a comparative ES between two or more treatments through a common comparator and is a natural extension of CMA (Higgins et al., 2012). A random-effects NMA was conducted in a frequentist framework. STATA software was used to conduct the analysis. As with the CMA process, the pooled ES of direct comparison between IE versus usual care and NIE versus usual care were presented with their corresponding 95% CI. Each treatment's estimated probability of being best was automatically produced from the software. This probability was the result of frequentist resampling methods, in which this probability was estimated by the proportion of samples in which the treatment ranked first.

Each outcome was conducted independently and involved a number of steps during the analysis process which were as follows:

1. Drawing the network map: the map is important in terms of showing a direct and indirect comparison between interventions. It also provides an illustration of the sample size of each group (represented by the size of node of each intervention).
2. Performing consistency analysis: In this action, the software makes estimated assumptions of consistency of multiple variants. Consistency analysis is an important step in the NMA process as it plays a part in ensuring the validity of results despite usual variations under the random effect model (Higgins et al., 2012).
3. Developing combined forest plots of different comparison arms: this is an essential part of the procedure to enable the calculation of comparative effects.
4. Producing a comparison summary: this involves the estimation of the ES of each intervention versus control (e.g. IE versus usual care or IE versus NIE). This comparison is the principal reason for the conduction of the analysis.
5. Producing probability ranking tables: these tables show the probability of each intervention being either best, second or worst among the interventions included in the analysis. The ranking of interventions was decided based on automatically-calculated Surface Under the Cumulative Ranking Curve (SUCRA) scores.

3.3.11 Sensitivity analysis

Sensitivity analyses were undertaken to evaluate the robustness of study results. This was done based on heterogeneity and consistency of meta-analysis results.

3.4 Results

3.4.1 Study selection for individualised exercise

The first systematic research review was performed from inception until December 2017. The search process is summarised in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) chart (Figure 3-1). The initial search, performed using the pre-set search strategy, resulted in 1,766 results across all included databases. After the removal of 514 duplicated entries 1,248 studies remained. Three further relevant studies were identified through searching the studies' reference lists.

The titles, abstracts, and full texts of the 1,251 studies were screened against the eligibility criteria. The first stage of eligibility assessment resulted in the removal of 1,202 studies. The second assessment stage, involving a thorough screening of the full texts of the remaining 49 studies, produced 17 studies that fulfilled the inclusion criteria. Eight of these 17 studies compared IE to usual care and were included in the meta-analysis. And the remaining nine studies were evaluated narratively. The search was updated in April 2020 and did not identify any additional studies for inclusion (Figure 3-3).

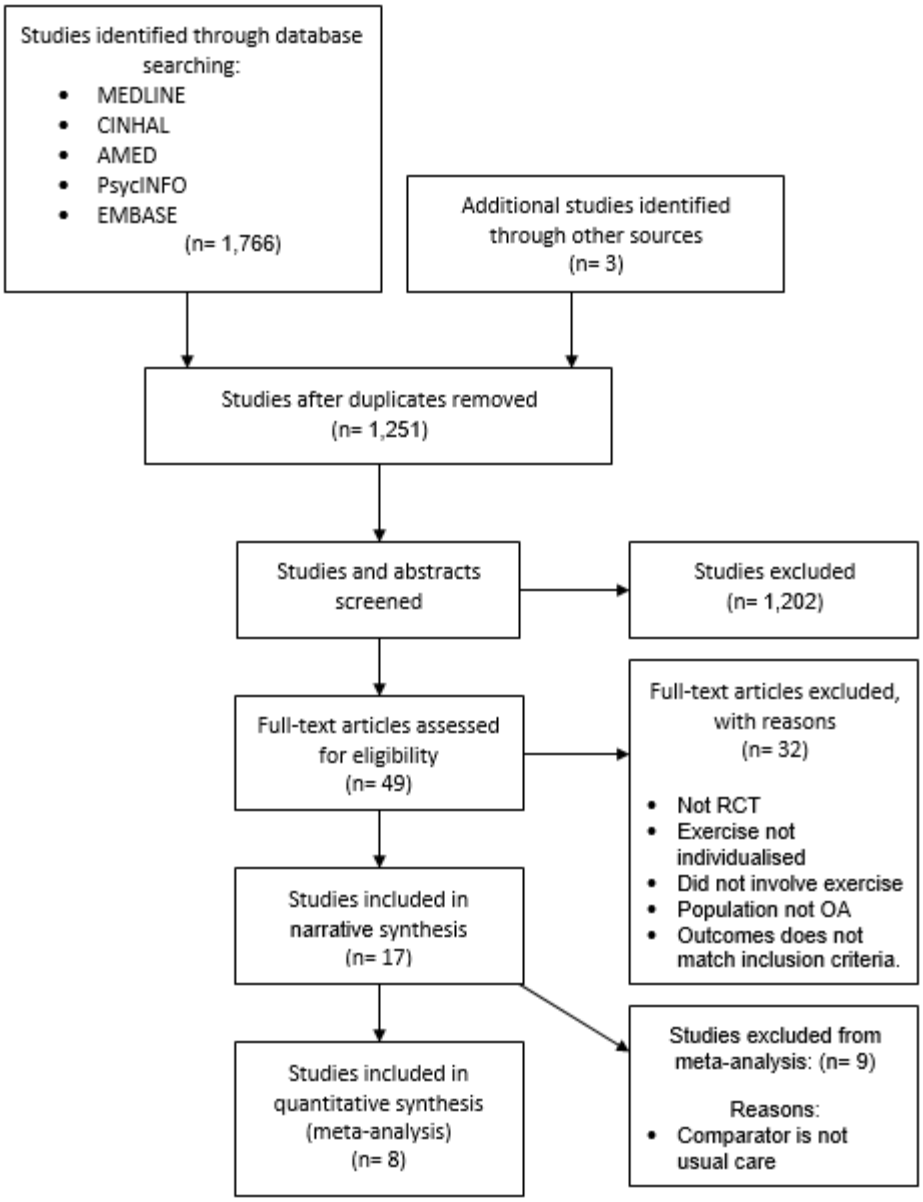


Figure 3-1. Individualised exercise search flow chart

RCT= Randomised controlled trials
OA= Osteoarthritis
N = Number

3.4.2 Study selection for non-individualised exercise

In December 2017, a systematic search for all exercise interventions for hip and knee OA was carried out across the following databases: MEDLINE, CINHAL, AMED, PsycINFO and EMBASE using pre-defined inclusion criteria (Goh et al., 2016). The search identified 13,629 studies, reported across multiple databases, in addition to 43 studies which were identified using other resources (Figure 3-2). Once all duplicate reports had been electronically removed, the titles and abstracts of the remaining 7,635 studies were screened. This initial screening process excluded 7,286 studies, while 349 studies progressed to the full-text screening stage. In the final screening process, 285 studies were excluded for various reasons, including the use of non-relevant interventions, the inclusion of non-relevant populations, non-relevant study designs, and the use of an interventional comparator. This left 64 studies for the quantitative synthesis.

The eligibility criteria for the full-text screening process was modified from the original systematic review (Goh et al., 2019b) to exclude studies that had individualised exercise interventions in order to get the NIE trials. The search for all exercise trials was updated in April 2020. Four new NIE studies for knee OA were identified (Figure 3-3).

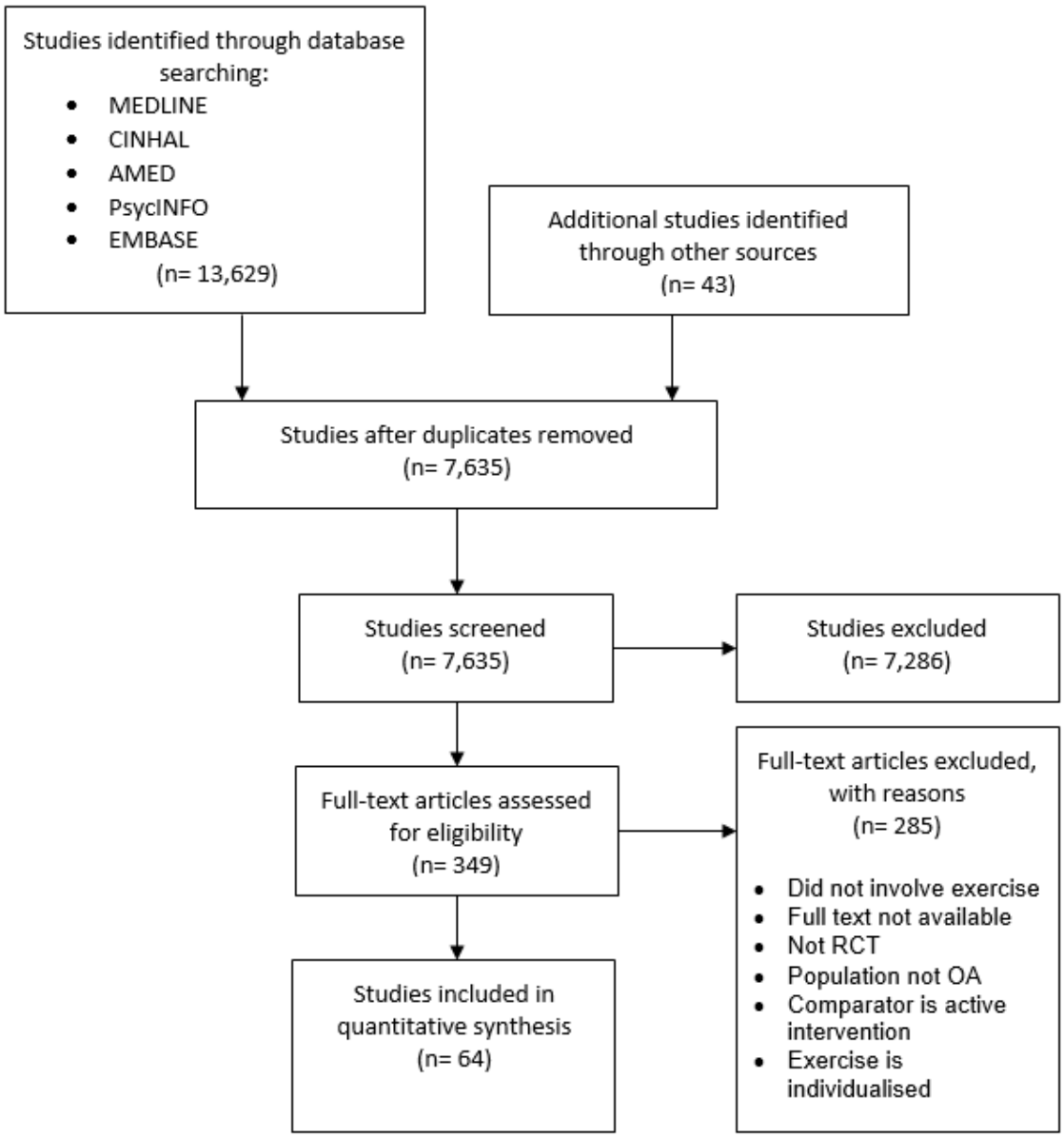


Figure 3-2. All exercise studies' search and identification of non-individualised exercise flow chart

RCT= Randomised controlled trials
OA= Osteoarthritis
N = Number

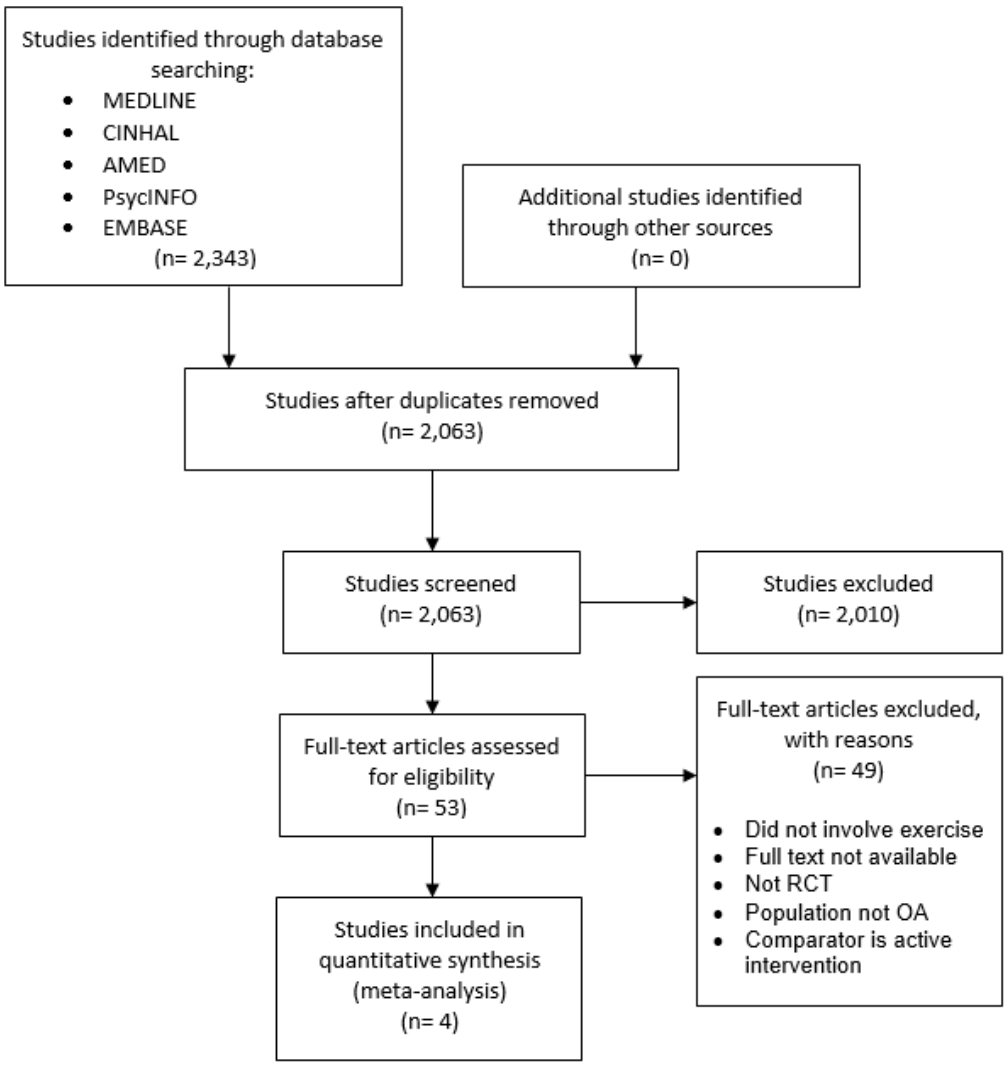


Figure 3-3. Search update for individualised and non-individualised exercise (Dec 2017- April 2020)

RCT= Randomised controlled trials
OA= Osteoarthritis
N = Number

3.4.3 Validation of screening and data extraction

Validation of screening was completed through re-screening a random selection of 20% of the titles identified in the search. No conflict was found between the original screening results and the validation by the second reviewer (BK).

The second reviewer (BK) undertook the same data extraction process on a randomly selected sample of 20% of the included studies. A comparison of these validation forms against the original extraction forms for the studies resulted in an agreement level of 92%. The 8% disagreement was resolved completely by consultation with the primary supervisor (MH).

3.4.4 Excluded studies

The list includes 32 studies subjected to full-text screening from the initial IE search and 53 studies subjected to full-text screening from the search update for both IE and NIE studies (Appendix 6: list of excluded studies).

The reasons for exclusion for each study were one or more of the following:

- The study was not an RCT (e.g., there was no control group or randomisation).
- The participants were not diagnosed with OA.

- The intervention did not involve exercise.
- Outcomes does not match inclusion criteria.

3.4.5 Characteristics of studies of individualised exercise

Among the 17 eligible studies, five were conducted before 2010. Most studies were conducted either in Europe (8) or North America (5). The total number of participants across all the studies was 2400, and the mean age of study participants was 63.7 years. Most of the funding for included studies came from public sources (13 studies). Studies used different methods to define OA, including the ACR grading system, KL radiographic criteria, duration of pain and other methods (Table 3-3).

In 11 of the studies, all sessions involving delivery of the intervention were directly supervised by physiotherapists or trainers, while six other studies provided a mix of supervised and non-supervised intervention (e.g., home-based, internet-based). One study did not provide sufficient details of the method of delivery (Cheing et al., 2002). Only one study included a specified educational component alongside the exercise intervention (Villadsen et al., 2013). The educational package in that study included written information about the expected progress of the condition, management options and a leaflet on various exercises targeting a range of motion and dynamic stability.

The studies evaluated the effects of exercise on a range of different outcomes. Pain outcomes were evaluated in all included studies using one of four scales, specifically: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al., 1988); the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos and Lohmander, 2003); a Visual Analogue Scale (VAS); and the Intermittent and Constant Osteoarthritis Pain score (ICOAP) (Hawker et al., 2008). Ten of the included studies had only two arms for comparison, three studies had three arms, and two studies had four arms. Comparison methods also varied, with seven studies comparing IE against no treatment or usual care. The rest of the studies used different types of intervention including electrical stimulation, sham exercise, intra-articular injections and others (Table 3-4).

Table 3-3. Summary of individualised exercise study characteristics

Study characteristics	No. of trials (%) (total=17)
Publication year	
2000-2009	5 (29.4)
2010 onwards	12 (70.5)
Study location	
Europe	8 (47)
North America	5 (29.4)
Asia	1 (5.8)
Australia	3 (17.6)
Language	
English	17 (100)
Source of funding	
Public	13 (76.4)
Non-public	1 (5.8)
Unclear	3 (17.6)
Participants	
Total number	2400
Median age (range) years	63.7
Diagnostic procedure[1]	
ACR	6 (35.2)
K/L grade	5 (29.4)
Duration of pain	1 (5.8)
Other	8 (47)
Method of delivery	
Supervised	11 (64.7)
Mixed supervised and non-supervised	2 (11.7)
Mixed supervised and home-based	3 (17.6)
Internet-based	1 (5.8)

[1]Some studies used more than one diagnostic criteria.
ACR= American College of Rheumatology
K/L= Kellgren and Lawrence
No. = Number

Table 3-4. Details of each study examining individualised exercise

Author	Country	N	Drop-outs	Diagnostic criteria	Arms of the study	Outcome measurement
(Brismee et al., 2007)	Australia	41	10	ACR	1. Tai Chi exercise (individualised) 2. Attention control	VAS for pain WOMAC function
(Allen et al., 2018a)	US	350	46	ACR	1. Supervised physiotherapy 2. Internet-based exercise training 3. Waiting list	WOMAC pain WOMAC function
(Beckwée et al., 2017)	Belgium	35	5	Duration of pain and K/L grade	1. Strengthening exercise 2. Walking exercise	ICOAP pain
(Cheing et al., 2002)	Hong Kong	62	10	K/L grade	1. Transcutaneous electrical nerve stimulation (TENS) 2. Placebo stimulation 3. Exercise 4. TENS and exercise	VAS for pain
(de Rooij et al., 2017)	US	126	19	ACR	1. Individualised exercise intervention 2. Current medical care	WOMAC pain WOMAC function

(Foroughi et al., 2011)	Australia	54	17	Symptomatic and radiographic assessment	1. Progressive individualised exercise intervention 2. Sham exercise	WOMAC pain Dynamic alignment and knee adduction moment
(French et al., 2014b)	US	131	17	Symptomatic and radiographic assessment	1. Exercise 2. Manual therapy and exercise 3. Control: usual care	WOMAC function NRS pain
(Knoop et al., 2014)	Netherlands	159	5	ACR	1. Experimental: proprioception training, strengthening exercise, and ADLs training 2. Control: strengthening exercise and ADLs training	WOMAC function NRS pain
(Lim et al., 2008)	Australia	107	10	ACR	1. Strength: mal-alignment in joint 2. Strength: no mal-alignment in joint 3. No treatment: mal-alignment in joint 4. No treatment: no mal-alignment in joint	WOMAC pain Peak external knee adduction moment

(Mikesky et al., 2006)	US	221	59	K/L grade	1. Strength training 2. Attention control (ROM exercise)	Muscle strength WOMAC pain
(Saccomanno et al., 2016)	Italy	165	8	ACR and K/L grade	1. Intra-articular injections of corticosteroids, HA 2. EBR (individualised) 3. Intra-articular injection HA + EBR	WOMAC function AROM
(Segal et al., 2015)	US	58	16	Symptomatic and radiographic assessment	1. Gait training intervention (individualised walking exercise) 2. Usual care	KOOS knee pain Late Life Function and Disability (LLFDI)
(Skou et al., 2015)	Denmark	100	19	Symptomatic and radiographic assessment	1. MEDIC treatment: education, exercise, (individualised) weight loss, pain medication, and insoles 2. Usual care	KOOS overall KOOS pain KOOS ADL Timed Up and Go test

(Villadsen et al., 2013)	Denmark	165	12	Symptomatic and radiographic assessment	1.	Neuromuscular exercise programme (individualised) in addition to educational programme	KOOS ADL KOOS walk test HOOS ADL HOOS walk test
					2.	Educational programme	
(Thorstensson et al., 2005)	Sweden	61	5	K/L grade	1.	Exercise group	KOOS overall KOOS pain KOOS performance KOOS ADL
					2.	Control group	
(Henriksen et al., 2014b)	Denmark	60	12	Symptomatic and radiographic assessment	1.	Individualised exercise group	KOOS pain KOOS function KOOS QoL
					2.	No attention control group	
(Hay et al., 2018)	United Kingdom	526	111	Clinical assessment	1.	Usual physiotherapy care	WOMAC pain WOMAC function
					2.	Individualisation of a lower limb exercise programme	
					3.	Support to adhere to longer-term general physical activity	

ACR= American College of Rheumatology. ADLs= Activities of Daily Living. ROM= Range of Motion. AROM= Active Range of Motion. EBR= Exercise-based rehabilitation. HA= Hyaluronic Acid. HOOS= Hip Injury and Osteoarthritis Outcome Score. ICOAP= Measure of Intermittent and Constant Osteoarthritis Pain. KOOS= Knee Injury and Osteoarthritis Outcome Score. K/L= Kellgren and Lawrence. LLFDI= Late Life Function and Disability Index. NRS= Numeric Rating Scale. TENS= Transcutaneous electrical nerve stimulation. VAS= Visual Analogue Scale. WOMAC= The Western Ontario and McMaster Universities Osteoarthritis Index.

3.4.5.1 *Characteristics of exercise types in studies of individualised exercise*

Among the 17 trials included in the review, five studies applied a strengthening exercise, two a prescribed aerobic exercise, one applied a mind–body form of exercise, and 11 studies involved a mixture of different types of exercise (Table 3-5).

Table 3-5. Types of exercise included in the 16 studies

Exercise type	No. of trials	No. of participants	Age median (range)
All types	17	2400	63.7 (50.6-70.8)
Strengthening	5	417	63.7 (60.1-67.2)
Aerobic	2	200	66.9 (65.3-67.2)
Mind–body	1	41	69.8
Mixed	11	1,945	62.2 (50.6-68.4)

The ways in which exercise was individualised varied considerably across the studies and are presented in Table 3-6. Ten studies prescribed different types or intensities of exercise based on specific characteristics, such as severity of symptoms and physical assessment. The individualisation process was based on pain severity in three studies and general physical assessment and performance in two studies, while one trial modified the intervention based on the presence of comorbidities

(Table 3-6). Six studies were included because they either stratified the randomisation process based on individual characteristics (such as age and BMI) or provided a subgroup analysis of the results according to specific participant characteristics. These studies were not included in the meta-analyses but were included in the narrative synthesis.

For eight of the 17 trials, the comparator or control arms involved no new active intervention, using instead either ongoing usual care, repeated observations while on a waiting list to enter a clinical trial or a sham exercise (placebo) intervention. The other nine studies used active interventions for the control group, including NIE programmes, intra-articular injections, and educational programmes.

Table 3-6. Intervention characteristics and reasons for inclusion/exclusion of individualised exercise studies in meta-analysis.

Author	Types of exercise	Mode of delivery	Duration (weeks)	Frequency	Method of Individualisation	Control	Inclusion in meta-analysis
(Brismee et al., 2007)	Tai Chi	Supervised (6 weeks) and home-based (6 weeks)	12	3/week	Randomisation was stratified by sex and age (>70 and <70). Results were reported separately for each group.	Active treatment.	Not included Control group received active treatment
(Allen et al., 2018a)	Strengthening exercise Stretching exercise Aerobic exercise	Supervised and internet-based	52	Unclear frequency for supervised sessions 3/week for internet-based	For the internet-based group, exercise difficulty was tailored according to pain severity, functional ability, and level of physical activity. Participants were assigned to one of 7 exercise difficulty levels.	Waiting list	Included
(Beckwée et al., 2017)	Strengthening exercise	Mixed: supervised	18	Unclear	Participants were stratified prior to allocation according to	Both arms included	Not included

	Walking exercise	and non-supervised			age, gender, and body mass ratio.	exercise programmes	Exercise was not individualised
(Cheing et al., 2002)	Isometric exercise	Unclear	4	5/week	Participants were stratified prior to allocation and subgroup analysis of results was performed.	Electrical stimulation	Not included Control group received active treatment
(de Rooij et al., 2017)	Muscle strength training Aerobic training ADL training Flexibility and stability exercises	Supervised	20	2/week	Exercise was tailored according to comorbid diseases: coronary disease, heart failure, diabetes mellitus type 2, COPD and BMI.	Current medical care	Included
(Foroughi et al., 2011)	Strengthening exercises	Supervised	24	3/week	Daily modification of exercise according to intensity of symptoms.	Sham exercise	Not included Control group received active treatment

(French et al., 2014b)	Strengthening exercises	Supervised	8	Unclear	Exercise was tailored according to individual patients' physical assessment findings.	Usual care	Included
(Knoop et al., 2014)	Proprioception strengthening ADL[3] training	Mixed: 2 sessions supervised and 5 home-based (every week)	12	7/week	Subgroup analysis of results was performed according to muscle strength.	Both arms included exercise intervention	Not included Exercise was not individualised
(Lim et al., 2008)	Home-based strengthening exercises	Supervised	12	5/week	Participants were stratified prior to allocation according to leg muscle strength, proprioceptive accuracy of the knee joint, varus-valgus knee joint laxity and patient-reported knee instability.	Unclear	Not included Comparator is not usual care.
(Mikesky et al., 2006)	Strength training ROM[4] exercise	12-month mixed supervised and home-	120	3/week	Intervention was stratified based on sex, radiographic OA and severity of pain.	ROM exercise	Not included Exercise was not individualised

	Isokinetic strengthening	based programme followed by 18-month home-based-only exercise programme			Subgroup analysis presented results based on stratification group.		
(Saccomanno et al., 2016)	Strengthening exercise Flexibility exercises	Supervised	24	5/week	Exercise was individualised according to knee compartment most involved in the degenerative process (medial or lateral tibiofemoral compartment; patellofemoral compartment).	Intra-articular injection	Not included Control group received an active treatment
(Segal et al., 2015)	Individualised gait training with biofeedback Individualised home exercise programmes	Supervised	12	2/week	Exercise was individualised based on evaluation of strength, flexibility, ROM, and gait analysis at baseline.	Usual care	Included

(Skou et al., 2015)	Multidimensional exercise program: Neuromuscular exercise; NEMEX[6]	Supervised	12	2/week	Exercise was individualised by progression according to pain intensity and quality of exercise performance achieved by each individual**.**	Usual care	Included
(Villadsen et al., 2013)	NEuroMuscular Exercise (NEMEX) Circuit programme (comprises four exercise circles, including aerobic and strengthening exercises). The training session consists of three parts: warming up, a	Supervised	8	2/week	Individualisation was achieved using progression through exercise difficulty levels according to participants' performance**.** Educational package was provided for participants in the interventional period of the intervention (8 weeks)	Educational programme	Included

	circuit program, and cooling down.						
(Thorstensson et al., 2005)	Strengthening exercise Endurance training	Mixed: supervised and non-supervised	6	2/week	Intensity was gradually and individually increased during the six weeks through increased lever arm or range of motion exercises. Participants were encouraged to exercise at the highest intensity possible without affecting performance.	No intervention	Included
(Henriksen et al., 2014b)	Functional individualised exercise.	Supervised	12	3/week	Pre-specified performance-based progression. Pre-specified differently for each type of exercise.	No attention control	Included

(Hay et al., 2018)	Strengthening Flexibility Balance	Supervised	72	Unclear	Individualisation was based on the findings of the physiotherapy assessment of each individual, Including: biomechanical and physiological observations, pain responses to specific exercises, starting levels of strength, range of movement and balance.	Usual physiotherapy care (including exercise)	Not included

ADL= Activities of Daily Living. BMI= Body Mass Index. COPD= Chronic Obstructive Pulmonary Disease. NEMEX=The NEuroMuscular EXercise training programme. OA= osteoarthritis. ROM= Range of Motion

3.4.6 Intervention description assessment of individualised exercise studies

The template for intervention description and replication (TIDieR) checklist was completed for all included IE studies (Table 3-7) and a summary is presented in Figure 3-4. The completeness of intervention reporting was assessed only for the intervention arm and not for the control. Only one of the included studies provided a complete description for all the items on the checklist (Hay et al., 2018). Two studies described 11 out of 12 items (Foroughi et al., 2011, de Rooij et al., 2017), and another study had 10 of the 12 items described (Allen et al., 2018a). The remaining study scores ranged between five and nine described items of the 12 items in the checklist. An intervention description assessment of 20% of the included studies was validated by an independent reviewer (AI). Validation showed 92% agreement and any disagreement was resolved by discussion.

All the studies provided a brief description or short name describing the intervention provided and the procedures of its delivery (Items 1 & 4). However, only six studies (35.2%) reported how the exercise was modified during the course of the study and only seven studies (47.05%) specified the location of the study and the exercise prescription. Eight (47.05%) studies failed to provide any rationale or theory explaining why their intervention might work.

With regards to reporting adherence to exercise, 11 studies (64.7%) presented adherence levels of their participants, while six studies did not present any detail on how they would measure adherence, nor any results of adherence to exercise. In this review's assessment of adherence description, retention rate was not counted as a measure of adherence to exercise. Adherence was reported as a percentage of adherence with prescribed exercise and attendance to sessions. In most studies, adherence to home exercise was measured using a self-reported exercise logbook or personal record of exercise. Some studies reported exact rates of adherence but did not describe how these rates were measured (Brismee et al., 2007).

Table 3-7. Score for the TIDieR checklist for each study

Author	*1.*	*2.*	*3.*	*4.*	*5.*	*6.*	*7.*	*8.*	*9.*	*10.*	*Adherence*		*Total*
	Intervention	*Rationale*	*Materials*	*Procedure*	*Person*	*Modes*	*Location*	*Frequency*	*Tailoring**	*Modified*	**11. Planned**	**12. Delivered**	
(Brismee et al., 2007)	✓	✓	✓	✓	✗	✓	✓	✓	✗	✗	✓	✓	9
(Allen et al., 2018a)	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	10
(Beckwée et al., 2017)	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	8
(Cheing et al., 2002)	✓	✓	✓	✓	✗	✗	✗	✓	✗	✗	✗	✗	5
(de Rooij et al., 2017)	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	11
(Foroughi et al., 2011)	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	11
(French et al., 2014b)	✓	✗	✗	✓	✓	✓	✓	✗	✓	✗	✓	✓	8

(Knoop et al., 2014)	✓	✓	✗	✓	✓	✓	✗	✓	✗	✗	✗	✓	7
(Lim et al., 2008)	✓	✓	✓	✓	✓	✓	✗	✓	✗	✗	✓	✓	9
(Mikesky et al., 2006)	✓	✗	✓	✓	✗	✓	✓	✓	✗	✗	✓	✓	8
(Saccomanno et al., 2016)	✓	✗	✗	✓	✓	✓	✗	✓	✓	✗	✗	✗	6
(Segal et al., 2015)	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✗	✗	9
(Skou et al., 2015)	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	9
(Villadsen et al., 2013)	✓	✗	✗	✓	✓	✓	✗	✓	✓	✓	✗	✗	7
(Thorstensson et al., 2005)	✓	✗	✗	✓	✓	✓	✗	✓	✓	✓	✓	✓	9
(Henriksen et al., 2014b)	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	11
(Hay et al., 2018)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	12

✓ = Yes, ✗ = No.

*Tailoring: Description of tailoring method is available in further supplementary table (Table 3-8).

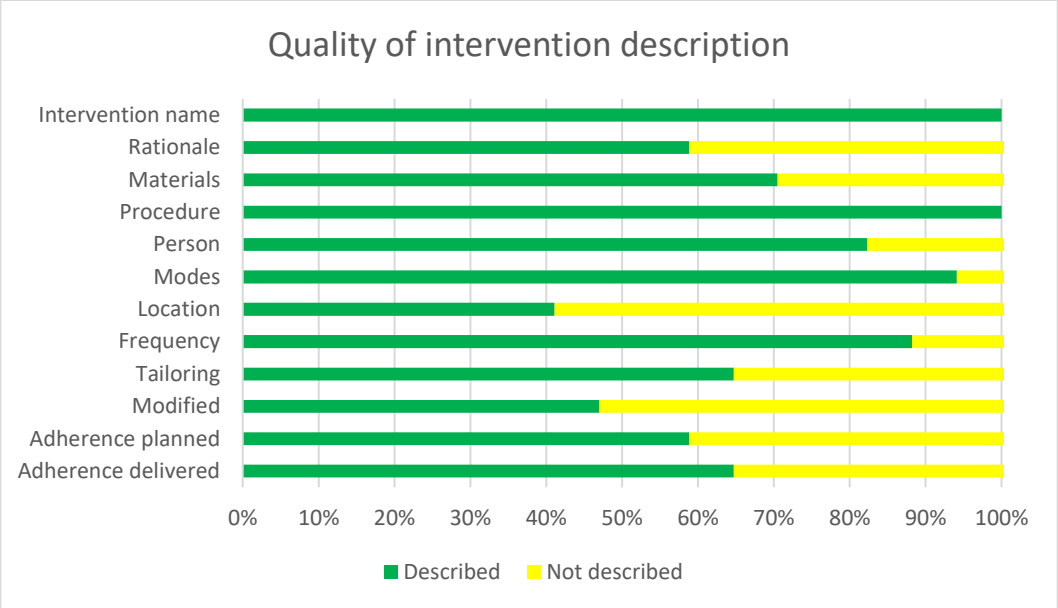


Figure 3-4. Summary of intervention quality assessment using TIDieR checklist

3.4.6.1 *Individualisation details*

Exercise was tailored to individual characteristics in 11 studies (Table 3-8). There was wide variation between the factors that were considered and how exercise was individualised (Figure 3-5). Three studies individualised exercise based on severity of OA symptoms, such as pain and decreased functional ability (Allen et al., 2018a, Foroughi et al., 2011, Skou et al., 2015). Three were based on performance-based adaptations (Henriksen et al., 2014a, Thorstensson et al., 2005, Villadsen et al., 2014). The remaining four studies each utilised a different method of prescribing an IE intervention, specifically: exercise tailored according to presence of comorbidities (de Rooij et al., 2017); exercise tailored according to assessment findings in two studies (French et al., 2014a, Hay et al.,

2018); exercise individualised according to which knee compartment was mostly affected (Saccomanno et al., 2016); and exercise tailored according to results of kinematic and kinetic gait analysis (Segal et al., 2015).

The description of the methods used to individualise exercise were generally poor in terms of detail. Five studies (55.5%) did not provide any rationale to explain why exercise was individualised. However, two studies provided thorough details about their intervention. The study by De Rooij et al. (2017) described exactly how the exercise was modified according to specific changes in comorbidities. The study team divided the participants according to their comorbidity types, such as coronary disease and heart failure. The individualisation methods were divided into three groups: the first group consisted of general adaptations which were applied to all participants; the second contained specified adaptations made for coronary disease patients; and the third involved specified adaptations made for participants with a history of heart failure.

For the general adaptations, the focus was first on testing the participant's maximum abilities by doing a maximum or symptom-limited exercise test. The researchers also used specific measures, such as maximum capacity expressed in watts (METs) and Borg Rating of Perceived Exertion (RPE) scale, to calculate the appropriate exercise intensity for each patient. The

individualisation programme specifically considered participants with poor health conditions, with the exercise provider undertaking close monitoring of such participants for signs of excessive strain. For the coronary disease group, specific education and coaching support was given to improve confidence and motivate participants to progress in their exercise. However, safety was critical and exercise was stopped immediately if the participant had any chest pain or other critical signs. The same conditions were applied for the heart failure group with multiple additional adaptations specified for this group. Prolonged warm-up and cool-down phases were used to decrease the risk of cardiac decompensation. Initial resistance training was given in order to reduce peripheral blood pressure and cardiac load before aerobic training. The participants were monitored for 3-4 hours after the exercise sessions to check for any critical change in vital signs. If recovery time was longer than expected, the training intensity was reduced.

The methods for individualising exercise were also well described in the study by Saccamanno et al. (2016). In this study, the participants were allocated to one of three exercise programmes based on knee mal-alignment (varus or valgus knees) and the compartment affected by radiographic OA (patellofemoral, medial tibiofemoral, lateral tibiofemoral). Each group received a specific training programme that aimed to

biomechanically assist load distribution and muscle balance to the specific knee malalignment of the participant.

The group with varus knee malalignment and medial tibiofemoral compartment OA were given stretching exercise specified for psoas, hip external rotators, medial flexors, biceps femoris and gastrocnemius muscles, and isometric and isotonic exercises for quadriceps and biceps femoris. The group with valgus knee malalignment and lateral tibiofemoral compartment OA were given stretching exercises but this was time tailored for psoas, medial flexors, biceps femoris and gastrocnemius. They were also given isometric and isotonic exercises for quadriceps, hip abductors and medial flexors. The group with patellofemoral arthritis received stretching exercises for the same muscles as the varus group with isometric exercises for quadriceps and isotonic exercises in a closed kinetic chain for quadriceps with elastic resistance. All groups received proprioceptive training alongside their exercise programme.

This level of detail was absent in most of the other studies where IE was not sufficiently described. For example, one of the included studies stated that exercise was individualised based on assessment findings (French et al., 2014b). However, no further information was available on what type of assessment this entailed, or the individual changes made to the exercise programme. Additionally, none of the studies that used IE based on OA

symptoms described sufficiently how this was achieved. No specific details were provided on what intensity levels for pain or ROM limitations were considered to modify the intervention. In addition, no clear description on how exactly exercise was modified based on variations of OA symptoms was given.

Table 3-8. Exercise individualisation details

Author	Description of individualisation method		
	What	Why	How
(Allen et al., 2018a)	Web-based exercise.	Not described	Exercise difficulty was tailored according to pain severity, functional ability and level of physical activity. Participants were assigned to one of seven exercise difficulty levels. Details of each difficulty level was not provided.
(de Rooij et al., 2017)	Exercise tailored according to presence of comorbidities.	Encourage and motivate OA patients with comorbidities to exercise in a safe and effective was.	Exercise was tailored according to comorbid diseases: coronary disease, heart failure, diabetes mellitus type 2, COPD and BMI. The authors provided detailed descriptions of adaptations made to the exercise programme based on changes in each comorbidity (Appendix 7: Adaptations to exercise programme)

(Foroughi et al., 2011a)	Daily modified exercise programme.	Not described	Exercises modified daily according to symptoms. Intensity of exercise was increased gradually if the pain level was low. If pain level was high, exercise intensity was lower than usual (within bearable limits). If pain was severe only isometric exercises were provided.
(French et al., 2014b)	Exercise tailored according to assessment findings.	Not described	The study indicated that the intervention was individualised according to "assessment findings". However, no details were provided about which specific assessment this applied to and how the exercise programme was modified.
(Saccomanno et al., 2016a)	Exercise was individualised according to knee compartment most involved in	Exercise should focus on restoring muscle balance and proper load distribution.	Three different exercise programmes were assigned to each of the following subgroups: 1- Varus knee (medial tibiofemoral compartment) 2- Valgus knee (lateral tibiofemoral compartment) 3- Patellofemoral osteoarthritis

	the degenerative process.		Details of exercise programme for each subgroup is available in Appendix 7: Adaptations to exercise programme
(Segal et al., 2015)	Individualised exercise and gait training programme.	Intensive individualised gait training with individualised exercise would decrease disability level and symptoms for prolonged period.	The kinematic and kinetic information in combination with clinical assessments of range of motion and strength were used to establish participant-specific goals. Gait training used real-time biofeedback to improve gait pattern. Individualised home exercise program was provided based on physical assessment of strength, range of motion and flexibility. No further details on the content of the exercise programme.
(Skou et al., 2015)	NEuroMuscular Exercise (NEMEX) training programme,	The purpose of individualising the intervention was to maintain the quality	Each participant was monitored individually with regard to pain intensity during the exercise session. Progression was allowed if the quality of the exercise could be maintained.

	involving multiple types of exercises, mainly strengthening and aerobic exercises, in high intensity but short duration.	of exercise performance.	
(Villadsen et al., 2013)	NEMEX training programme, involving multiple types of exercises, mainly strengthening and aerobic	Not described	Individualisation was achieved using progression through exercise difficulty levels according to participants performance.

	exercises, in high intensity but short duration.		
(Thorstensson et al., 2005)	Individualised high- intensity exercise programme including balance, aerobic and strengthening exercises.	Not described	Intensity was gradually and individually increased during the six weeks through increased lever arm or range of motion exercises. Patients were encouraged to exercise at the highest intensity possible without affecting performance.

(Henriksen et al., 2014b)	Functional individualised exercise.	Not described	Pre-specified performance-based progression. Pre-specified differently for each type of exercise. All exercises had several levels of difficulty. The physical therapist supervised each participant individually and adjusted the exercises and progression in difficulty individually during the entire course of the programme. Progression was decided based on participants' performance. Detailed progression instruction was provided for each type of exercise.
(Hay et al., 2018)	Strengthening Flexibility Balance	Exercise should be progressed so that appropriate physical stress is placed on the individual for further	The study included 2 arms of individualised exercise: 1- Individually tailored exercise: Individualisation was based on the findings of the physiotherapy assessment of each individual, Including: biomechanical and

	improvements to be obtained.	physiological observations, pain responses to specific exercises, starting levels of strength, range of movement and balance. 2- Targeted exercise adherence: general physical activity adherence over time. In addition to prescribing an individualised, progressed and supervised lower limb exercise programme, physiotherapists were trained to assess patients' current general physical activity levels, their intentions to increase their physical activity levels and their attitudes to exercise for knee pain and general health, as well as exploring their individual barriers to and potential facilitators of exercise.

BMI= Body Mass Index
COPD = Chronic obstructive pulmonary disease
OA= Osteoarthritis

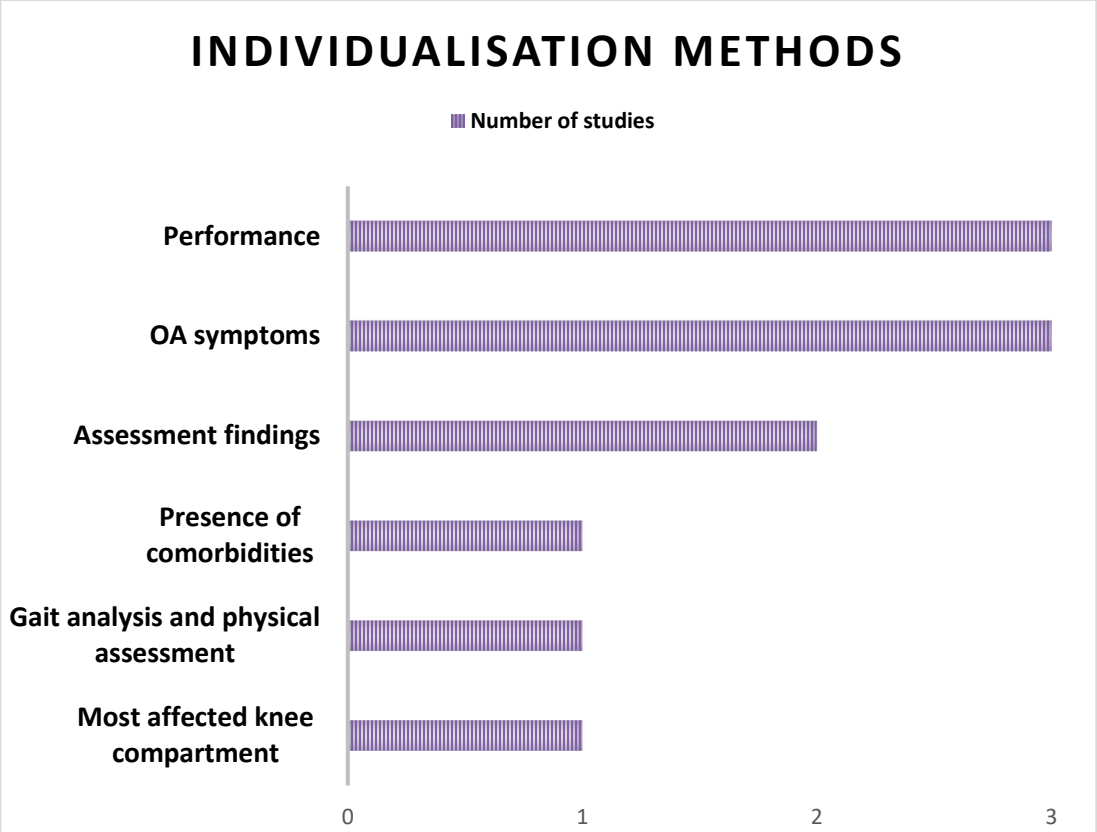


Figure 3-5. Summary of individualisation factors

3.4.7 Risk of bias assessment for individualised exercise studies

The quality appraisal of the individual studies is presented in Table 3-9 and a summary is presented in Figure 3-6. Clear variations in quality can be seen in both the conduct and reporting of trials. Blinding of participants is not feasible in exercise studies so none of the included studies blinded the participants. Five studies reported the assessor's blinding and one study reported the clinician's blinding. The study that blinded the clinicians stated that the clinicians were blinded to the outcome measures, and not to the intervention (Brismee et al., 2007). Adequate randomisation and

concealment of allocation were present in the majority (90% and 70%, respectively) of the included studies, indicating good quality in terms of planning and conduct of the trials. Additionally, 100% of studies reported the outcomes as pre-specified and homogeneity was present in the baseline characteristics of participants. Attrition rate was less than 15% in eight studies (47%) while intention to treat analysis was conducted in only seven studies (41%).

Risk of bias assessment was validated via an independent reviewer (AI). Validation resulted in 90% agreement. Points of disagreement were resolved by discussion.

Table 3-9. Risk of bias assessment

Author	*1. Randomisation*	*2. Allocation Concealment*	*3. Participants' blinding*	*4. Clinician blinding*	*5. Assessors' blinding*	*6. Attrition Rate <15%*	*7. Outcomes reported as Pre-specified*	*8. ITT* analysis*	*9. Similar baseline measures*	***Total out of 9***
(Allen et al., 2018a)	✓	✓	✗	✗	✓	✓	✓	✓	✓	7
(Beckwée et al., 2017)	✓	!	✗	✗	✗	✓	✓	✗	✓	4
(Cheing et al., 2002)	!	!	✗	✗	✗	✗	✓	✗	✓	2
(de Rooij et al., 2017)	✓	!	✗	✗	✓	✓	✓	✓	✓	6
(Foroughi et al., 2011)	✓	✓	✗	✗	✗	✗	✓	✗	✓	4
(French et al., 2014b)	✓	✓	✗	✗	✗	✗	✓	✓	✓	5
(Knoop et al., 2014)	!	!	✗	✗	✗	✓	✓	✓	✓	4

(Lim et al., 2008)	✓	✓	✗	✗	✗	✓	✓	✗	✓	5
(Mikesky et al., 2006)	✓	✓	✗	✗	✗	✗	✓	✗	✓	4
(Saccomanno et al., 2016)	✓	✓	✗	✗	✗	✓	✓	✓	✓	6
(Segal et al., 2015)	✓	✓	✗	✗	✗	✗	✓	✗	✓	4
(Skou et al., 2015)	✓	✓	✗	✗	✗	✗	✓	✓	✓	5
(Villadsen et al., 2013)	✓	✓	✗	✗	✗	✓	✓	✗	✓	5
(Thorstensson et al., 2005)	✓	✓	✗	✗	✗	✓	✓	✗	✓	5
(Brismee et al., 2007)	✓	!	✗	✓	✓	✗	✓	✗	✓	5
(Henriksen et al., 2014b)	✓	✓	✗	✗	✓	✗	✓	✗	✓	5
(Hay et al., 2018)	✓	✓	✗	✗	✓	✗	✓	✓	✓	6

✓ = Yes ✗ = No ! = Unclear

*ITT= Intention to treat analysis

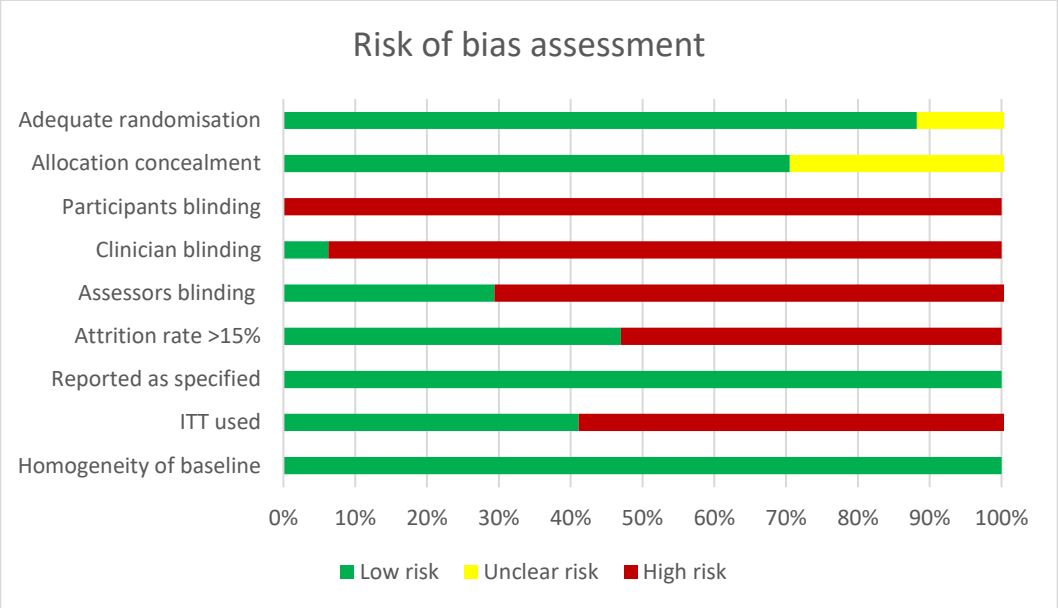


Figure 3-6. Summary of risk of bias assessment results

3.4.8 Adverse events of individualised exercise studies

None of the studies reported any serious adverse events. A number of included trials reported a minimal increase in joint pain and muscle soreness immediately after exercise (Allen et al., 2018a, Villadsen et al., 2014, Brismee et al., 2007, Foroughi et al., 2011), and in one study (Mikesky et al., 2006) one participant withdrew from the study due to post-exercise pain.

3.4.9 Characteristics of studies of non-individualised exercise

The review included 68 studies that compared exercise without individualisation to usual care. These studies included a total of 6,605 participants, of which 73.2% were women. The age range was between 41 - 84 years with a median age of 65 years. Most studies used ACR criteria for OA as inclusion criteria for participants (47%) while 38% of the studies used the K/L grading system (grade 2 or more). All included studies assessed outcomes of pain and performance while 65 assessed change to functional ability and only 34 assessed change to QoL (Table 3-10). Further details regarding the study characteristics can be found in the original paper (Goh et al., 2019b).

Table 3-10. Summary of study characteristics of non-individualised exercise studies

Summary of study characteristics	Total (n=68)
Participants	
Total number	6,605
Median age (range), years	66 (41.2-84.4)
Women (%)	4,086 (73.2%)
Diagnostic procedure	
ACR	32 (47%)
K/L grade	26 (38.2%)
Other	10 (14.7%)
Outcomes	
Pain	68 (100%)
Function	65 (95.5%)
Performance	68 (100%)
QoL	34 (50%)

ACR= American College of Rheumatology
K/L= Kellgren and Lawrence
QoL= Quality of Life

3.5 Conventional meta-analysis results

3.5.1 Individualised exercise

Using a standardised mean difference, the estimated ES across all studies was calculated for continuous data (pain, functional outcome, performance and QoL). The change in magnitude of ES from baseline to eight weeks (or the nearest to eight weeks) was calculated for all studies.

3.5.1.1 ***Pain***

Eight studies compared the effect of IE on pain outcomes relative to usual care. Six of these found significant improvements in the intervention group, while two studies reported that the change was not significant. The overall ES of IE was 1.00 (95% CI 0.35, 1.65) (Figure 3-7). The level of heterogeneity was considerable as the I^2 value shows (I^2 = 94.6%).

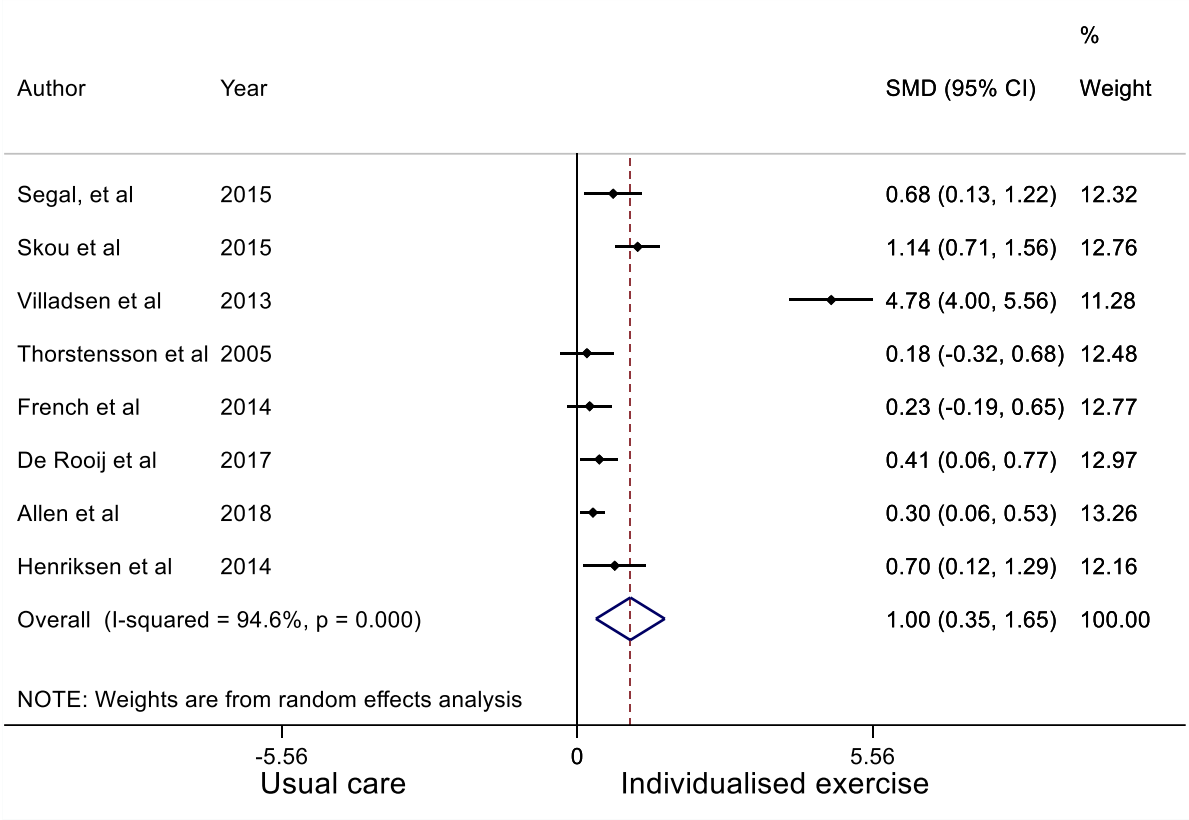


Figure 3-7. Forest plot of the effect of individualised exercise on pain at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.

3.5.1.2 ***Function***

Eight studies measured functional outcomes of IE for OA patients. Four studies reported a significant improvement in function with IE intervention. However, three studies reporting a positive change found no significant difference in comparison to usual care. The overall ES for IE was 1.23 (95% CI 0.45, 2.01) (Figure 3-8). The level of heterogeneity was also considerable in this outcome as the I^2 value was high (I^2 = 96%).

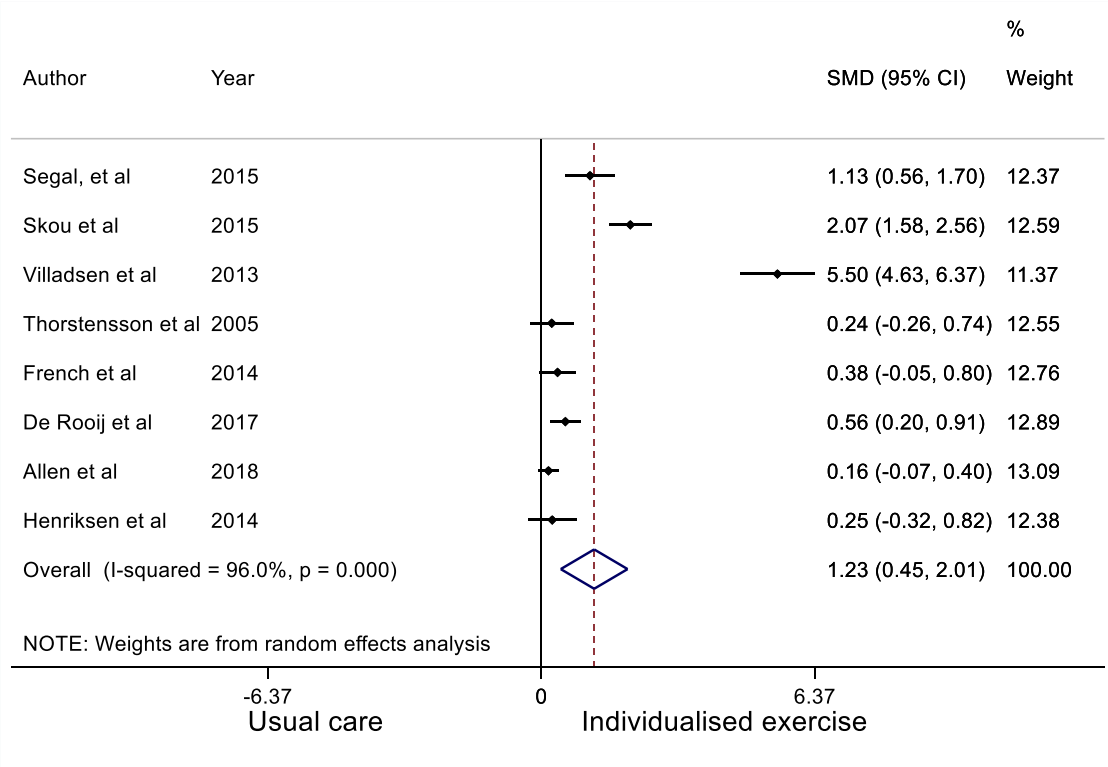


Figure 3-8. Forest plot of the effect of individualised exercise on function at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.

3.5.1.3 ***Performance***

Only three studies reported objective performance measures as outcomes. Two studies demonstrated significant improvement in performance outcomes while the third showed only limited (not significant) improvement with an overall ES of 1.37 (95% CI -0.21, 2.95) (Figure 3-9). Again, the heterogeneity level was considerably high (I^2 = 97.2%).

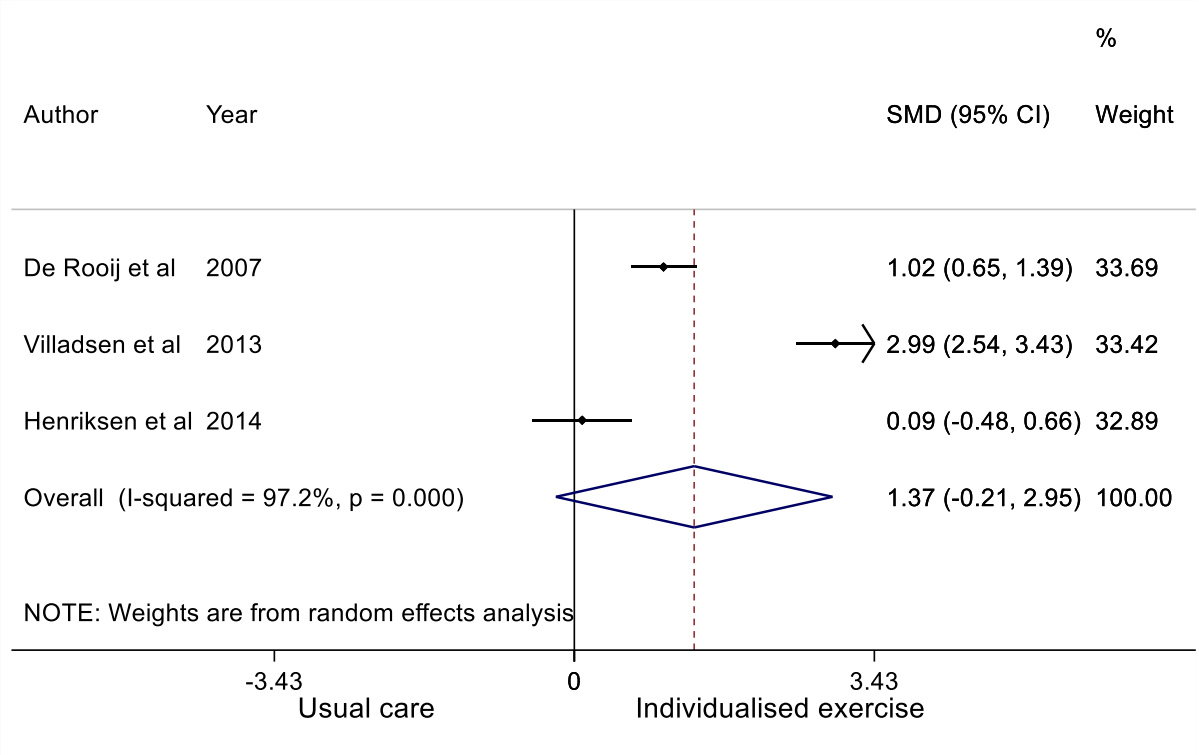


Figure 3-9. Forest plot of the effect of individualised exercise on performance at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.

3.5.1.4 *Quality of life (QoL)*

QoL outcomes were presented in three of the included studies. Although the overall change in QoL with IE was positive, this was not significantly better than usual care (ES 1.01 95% CI -0.30, 2.32) (Figure 3-10). A considerable level of heterogeneity was noted (I^2 = 95.4%).

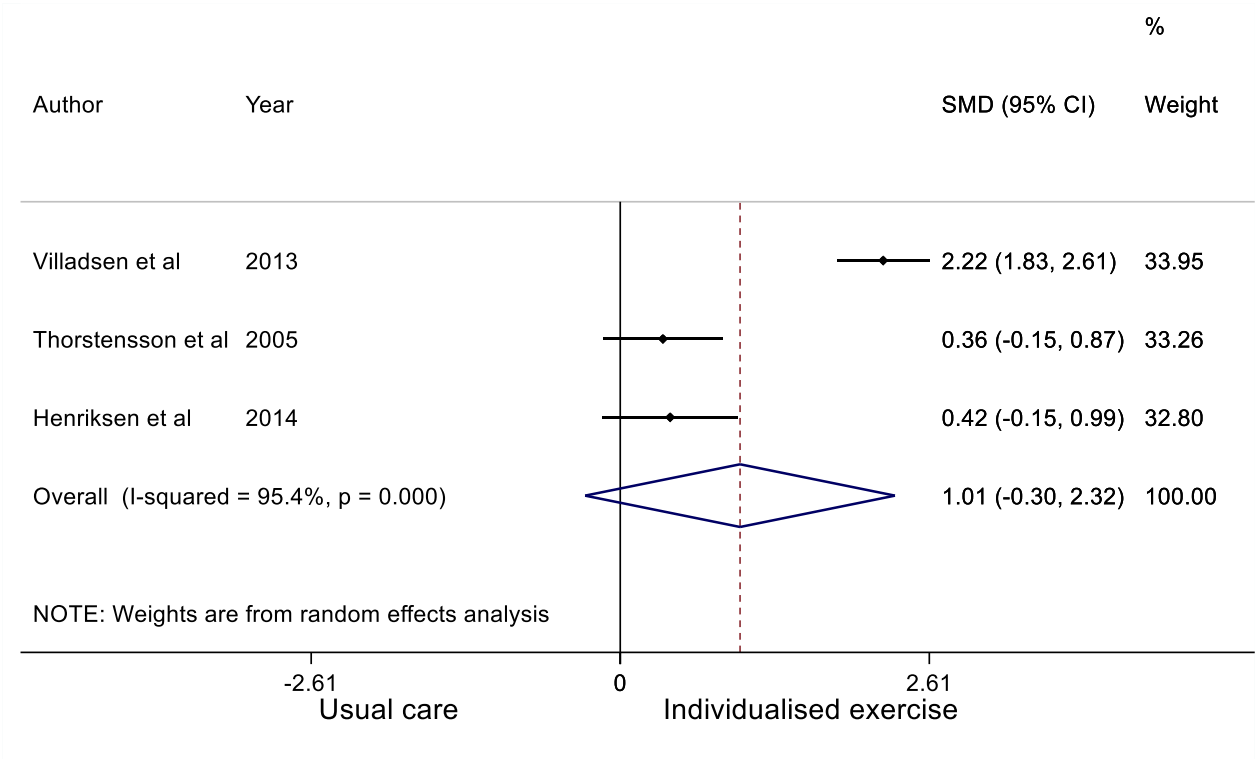


Figure 3-10. Forest plot of the effect of individualised exercise on quality of life at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.

3.5.2 Non-individualised exercise

Alongside the analysis of the effects of IE, a meta-analysis was undertaken to pool the results of studies on the effects of NIE on knee and hip OA. The analysis evaluated the effect of NIE on four main outcomes: pain, function, performance and QoL. Using SMD, the estimated ES across all studies was calculated for continuous data. The time point for all data in the analyses below was eight weeks, or the reported follow-up time point closest to eight weeks.

3.5.2.1 *Pain*

68 studies evaluated the effect of NIE on pain compared with usual care. NIE was found to have a positive effect in reducing pain outcomes, and to be significantly better than usual care (ES 0.58, 95% CI 0.46, 0.71) (Figure 3-11). The I^2 score was equal to 75%, which suggest a substantial level of heterogeneity.

3.5.2.2 *Function*

The effect of NIE on functional outcomes was presented in 65 clinical trials. In this category, the overall effect was similarly beneficial, and significantly better than usual care (ES 0.53, 95% CI 0.40, 0.65) (Figure 3-12). However, the heterogeneity level was substantial (I^2 = 74.6%).

3.5.2.3 *Performance*

NIE was reported to have a significantly greater effect on performance than usual care, as demonstrated in the pooled results of 68 trials (ES 0.52, 95% CI 0.39, 0.64) (Figure 3-13). A substantial level of heterogeneity was also noted for this outcome (I^2 = 72.4%).

3.5.2.4 *QoL*

The effect of NIE on quality of life was examined in 34 studies but was found not to be significantly better than usual care (ES 0.33, 95%CI 0.17, 0.49) (

Figure 3-14). The heterogeneity score was substantial (I^2 = 73.6%).

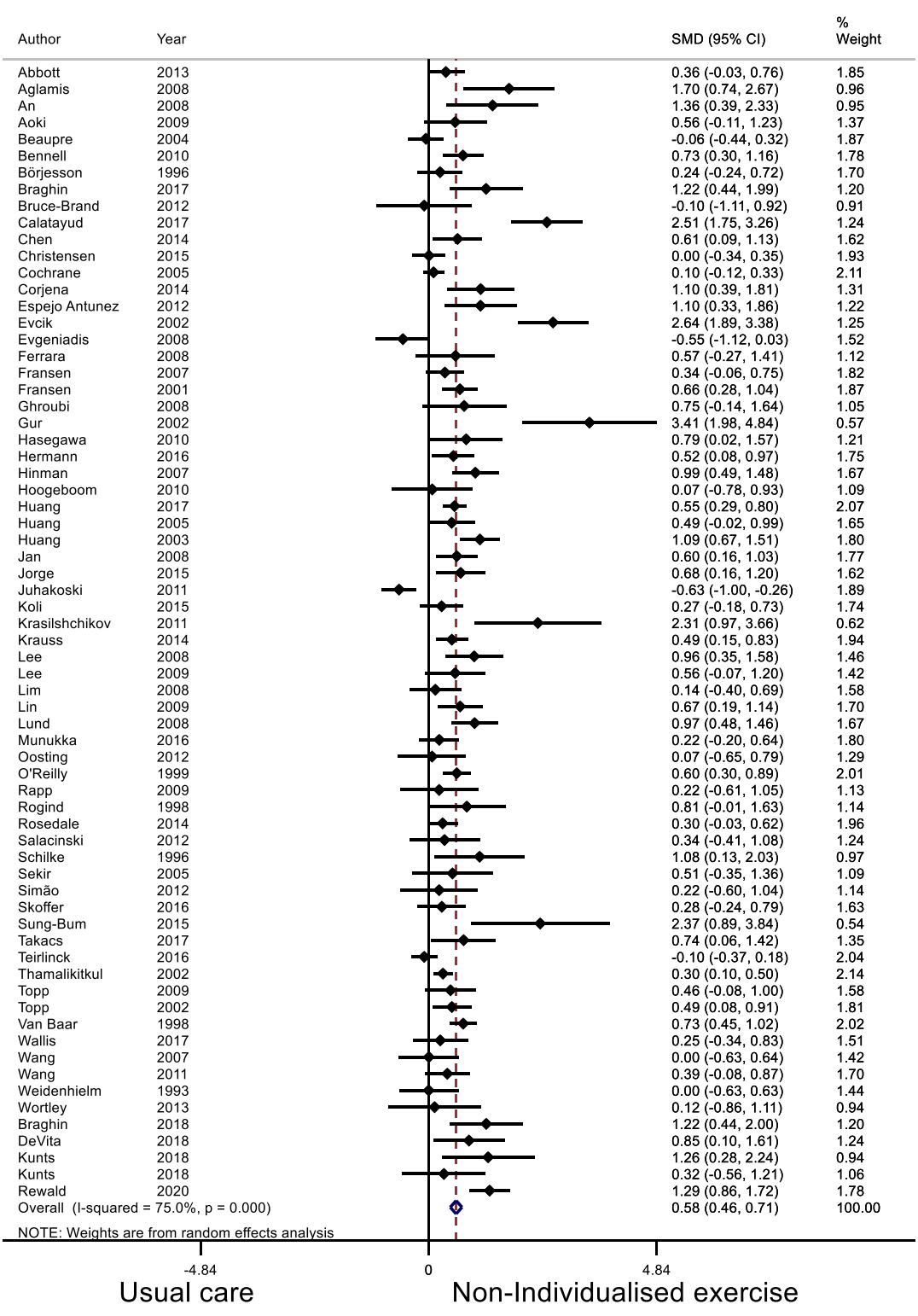


Figure 3-11. Forest plot of the effect of non-individualised exercise on pain at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.

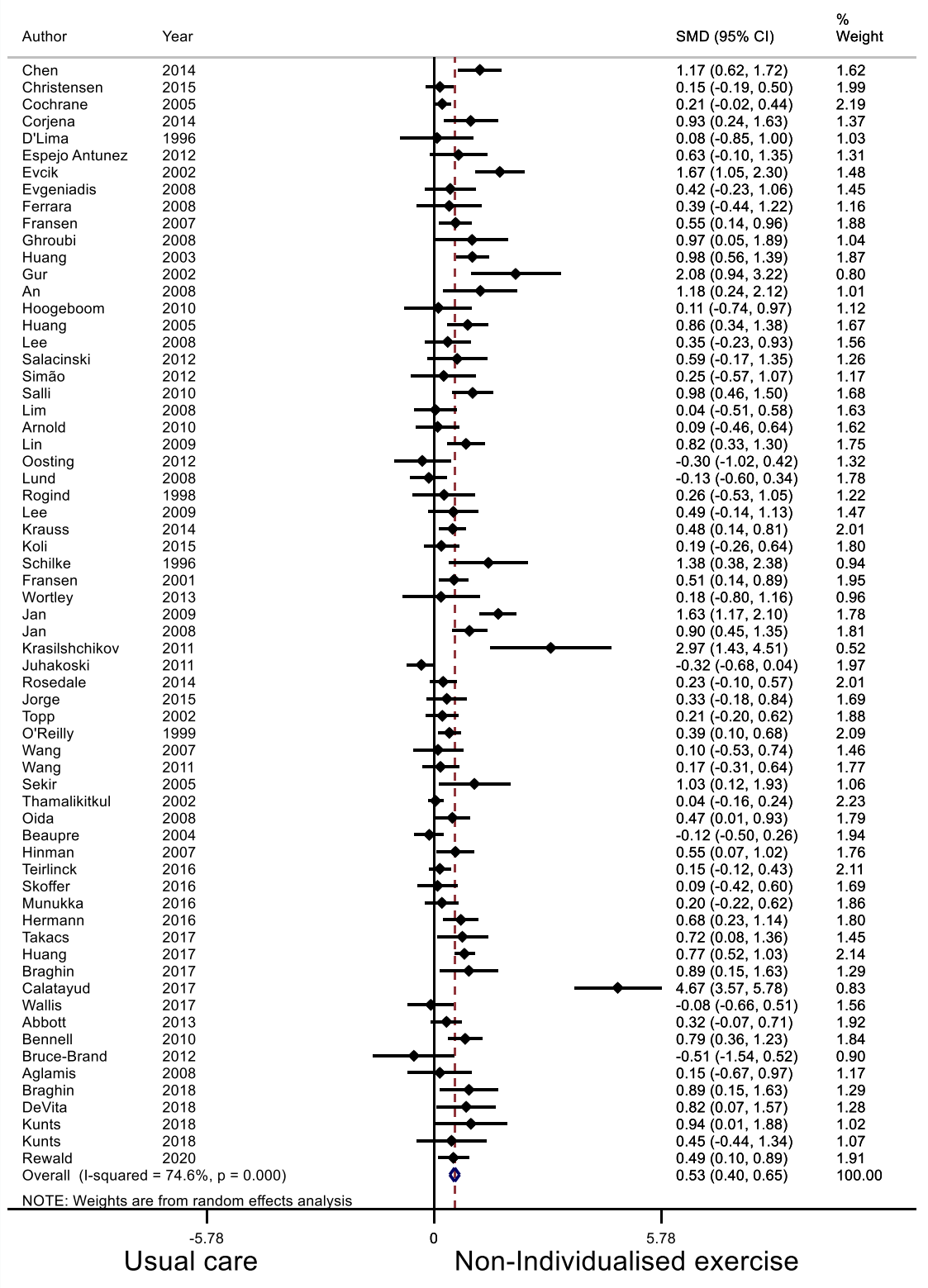


Figure 3-12. Forest plot of the effect of non-individualised exercise on function at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.

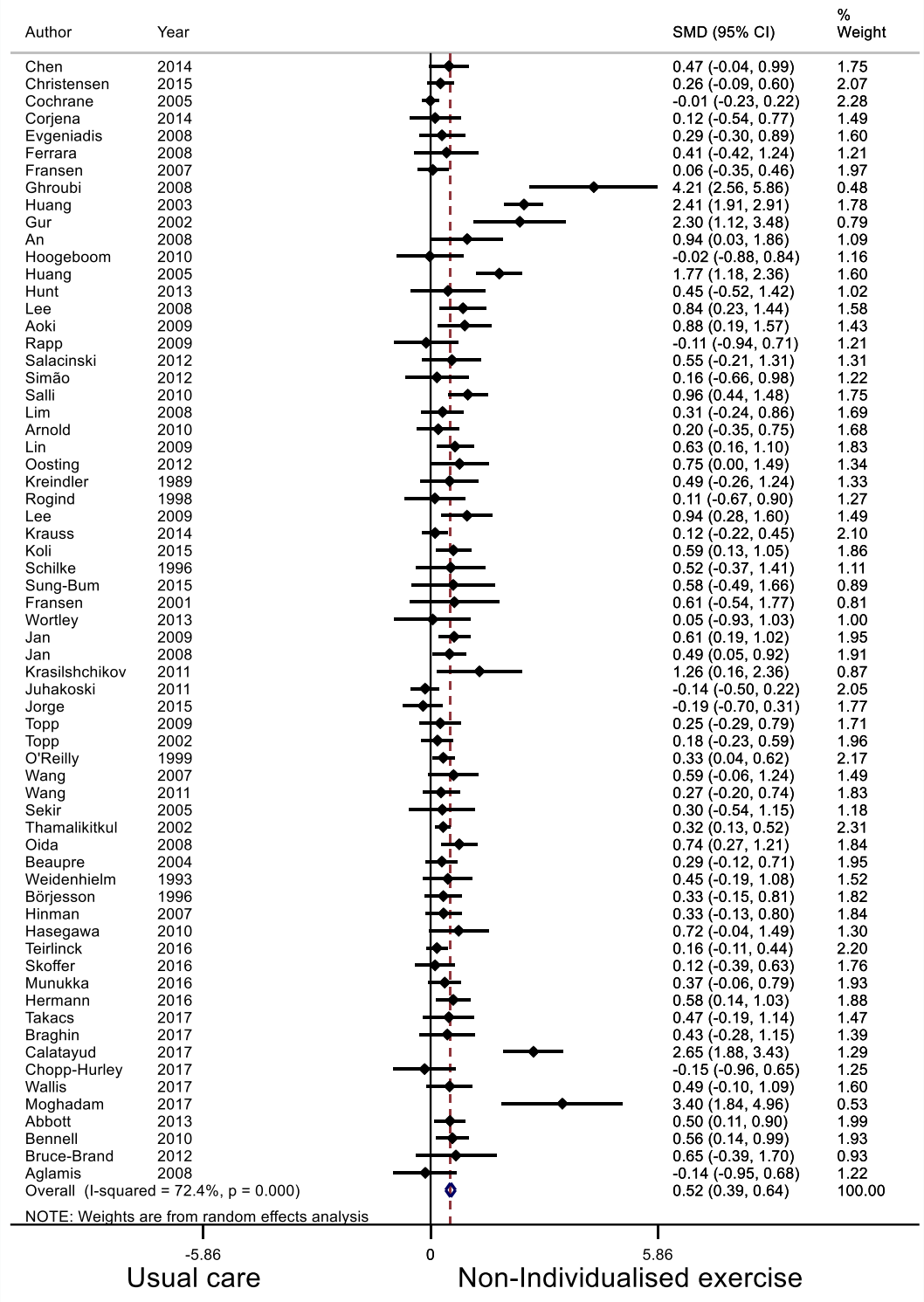
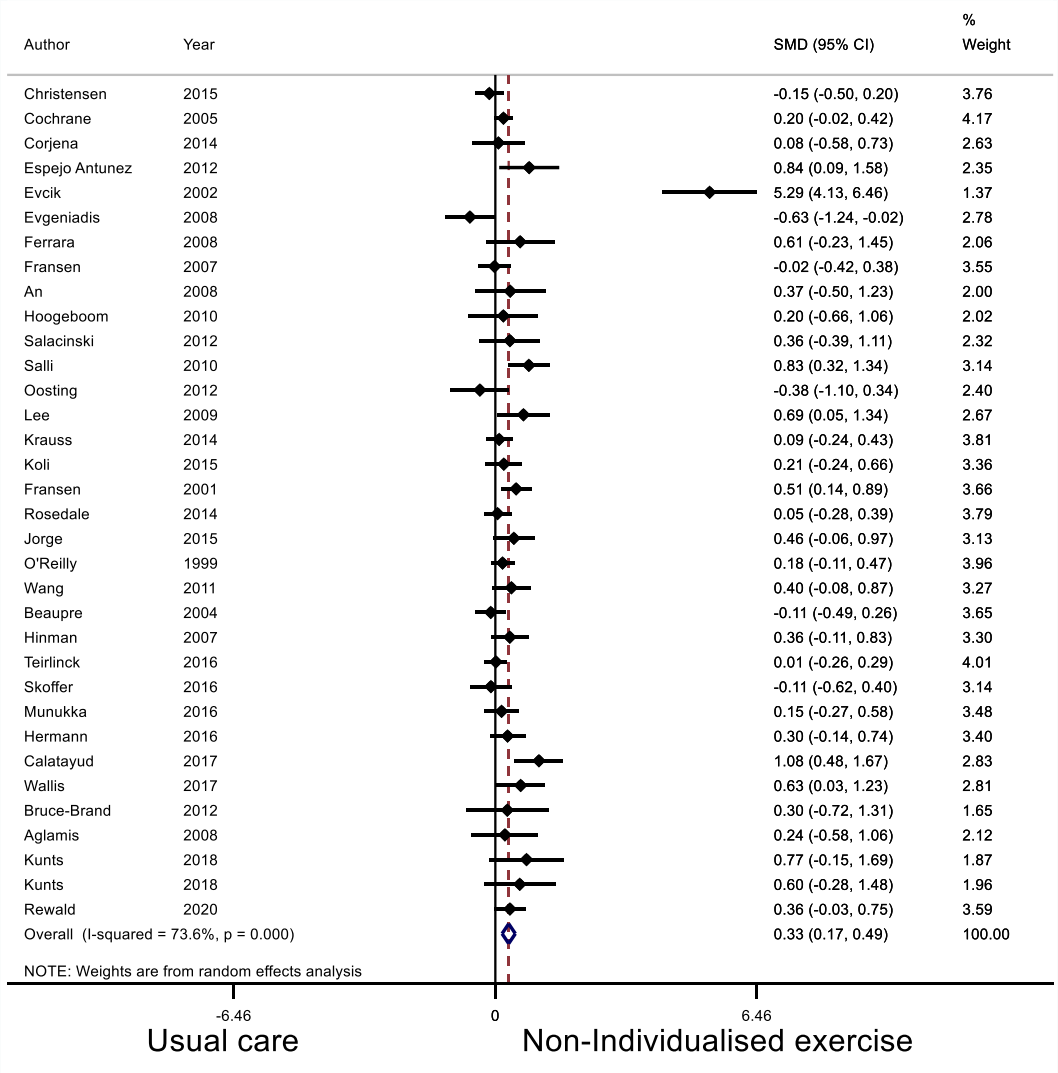


Figure 3-13. Forest plot of the effect of non-individualised exercise on performance at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.

Figure 3-14. Forest plot of the effect of non-individualised exercise on quality of life at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.



3.5.3 Publication bias for individualised exercise

The funnel plot below shows the assessment for publication bias for IE on pain outcomes. The evidence from the included studies is symmetrically distributed except for one outlying study (Villadsen et al., 2013). The data from this study were double-checked to ensure no error was made during the data extraction. The funnel plot (Figure 3-15) shows the publication bias for pain analysis in IE studies. Most of the studies showed a normal distribution, hence a low risk of publication bias, except for one study that had a significantly higher SMD than the other studies (Villadsen et al., 2013).

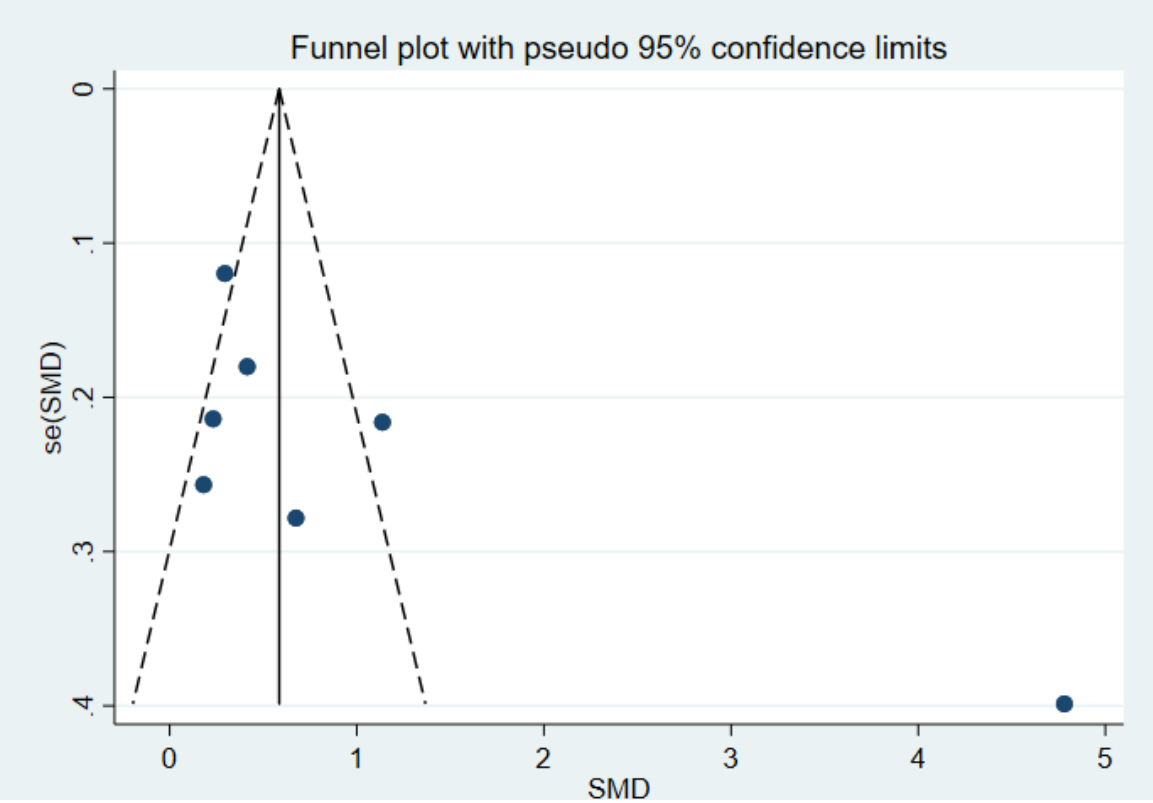


Figure 3-15. Funnel plot of individualised exercise for pain outcomes

3.5.4 Summary of conventional meta-analysis results

The ES of IE versus usual care was consistently greater than the ES of NIE versus usual care across all outcomes apart from QoL. However, estimate accuracy was not high enough to allow definite conclusions to be drawn, since IE had wide 95% CIs which overlapped with those for NIE (Table 3-11).

Table 3-11. Meta-analysis results summary

Outcome	Type of exercise	ES	95% CI	No. of studies (No. of participants)
Pain	IE	1.00	0.35 - 1.65	8 (991)
	NIE	0.58	0.46 - 0.71	68 (6,072)
Function	IE	1.23	0.45 - 2.01	8 (991)
	NIE	0.53	0.40 - 0.65	65 (5,829)
Performance	IE	1.37	0.21 - 2.95	3 (291)
	NIE	0.52	0.39 - 0.64	68 (6,009)
QoL	IE	1.01	-0.30 - 2.32	3 (226)
	NIE	0.33	0.17 - 0.49	34 (3,258)

ES= Effect size. CI= Confidence Interval. No. = Number. IE= Individualised Exercise. NIE= Non-Individualised Exercise. QoL= Quality of Life.

3.5.5 Sensitivity analysis

The study by Vialldsen et al. (2013) had significantly higher ES than the average ES of IE studies. Therefore, this study was identified as an outlier. Sensitivity analysis with removal of Vialldsen study results was done for ES of IE on pain outcomes. The analysis show that IE is still significantly better than usual care (ES = 0.50, CI 95% = 0.25, 0.75). Additionally, level of heterogeneity has dropped from (I^2 = 94.6%) to (I^2 = 60.8%) with removal of the outlier study (Figure 3-3-16).

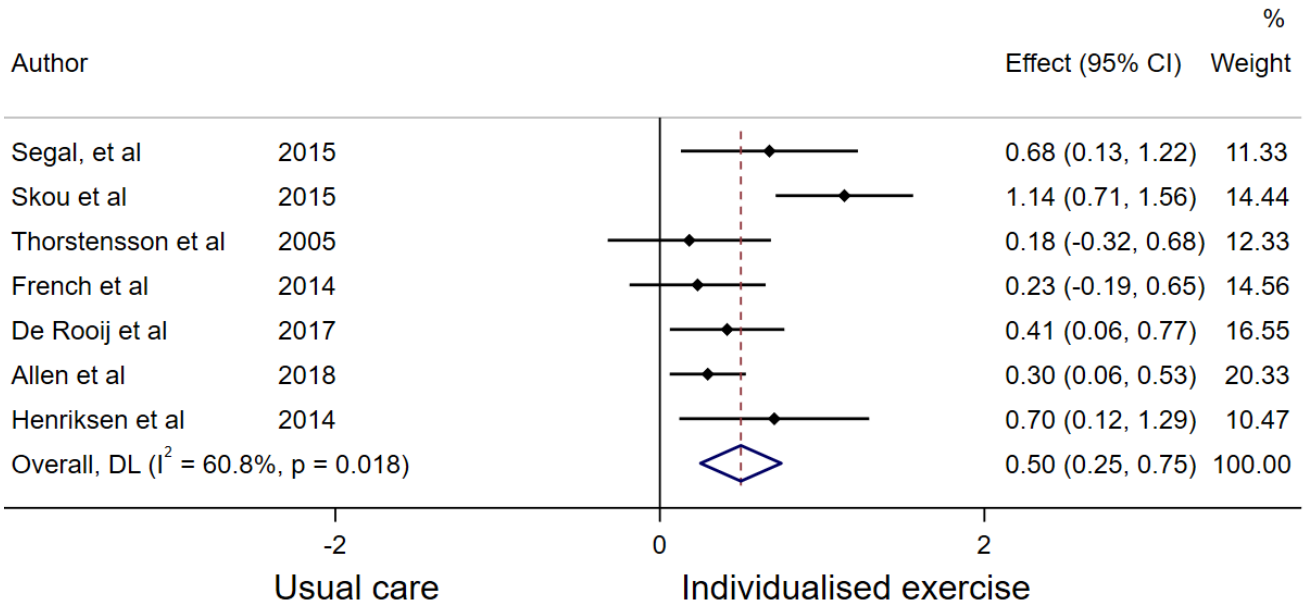


Figure 3-3-16. Sensitivity analysis forest plot of the effect of individualised exercise on pain at, or close to, 8 weeks

Effects are shown with 95% confidence intervals (95% CI). SMD: standardised mean difference.

3.6 Network meta-analysis results

3.6.1 Network diagram

Figure 3-17 represents the network of analytic comparison between IE, NIE and usual care for OA management. Each network represents the comparison for a different outcome. The node size reflects the number of participants in each group, which clearly shows that the sample size of the NIE group is considerably higher than the IE group. It is also apparent that the number of studies in both function and pain networks is higher than those in the network of performance and QoL.

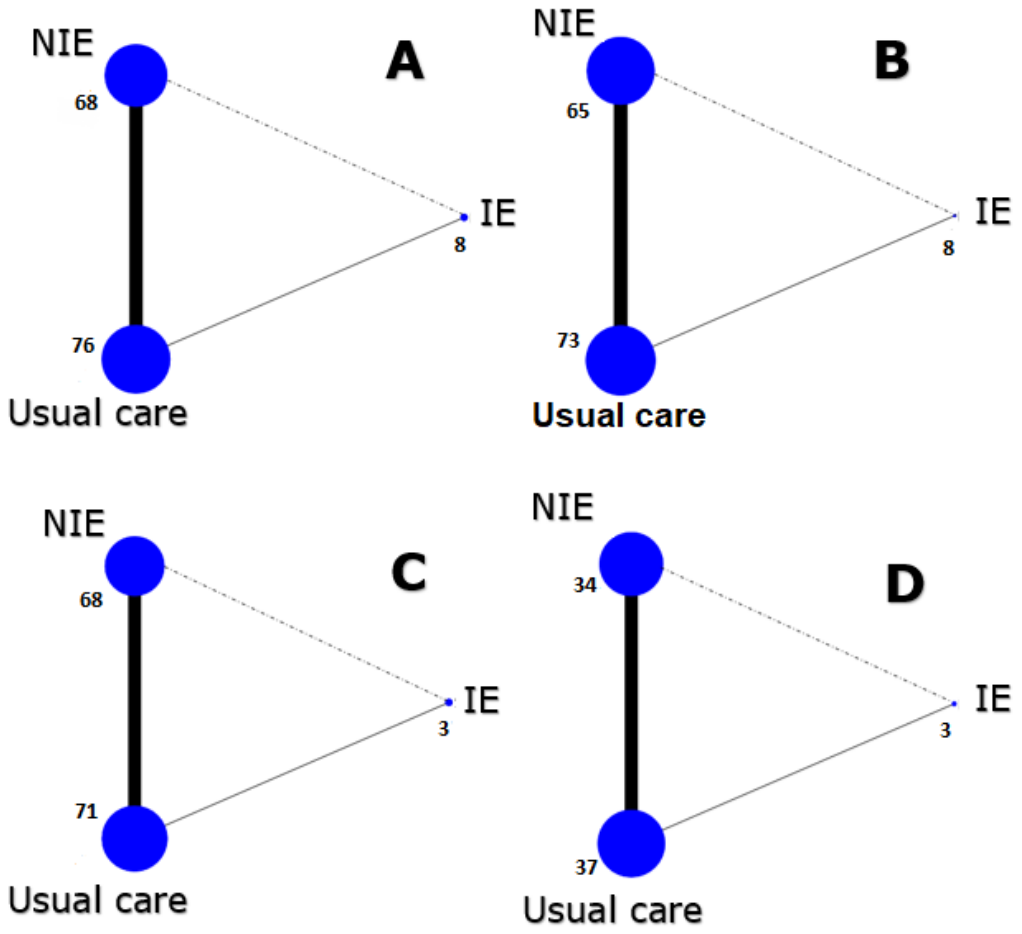


Figure 3-17. Network meta-analyses maps.

Showing the network of comparisons between individualised exercise (IE), non-individualised exercise (NIE) and usual care (UC). The straight line shows comparison for direct evidence and the dotted line shows comparison for indirect evidence. The number refers to number of studies in each group. The maps present the analyses of four outcomes: A- pain, B- Function, C- Performance and D - Quality of life.

3.6.2 Comparison between individualised exercise and non-individualised exercise

The efficacy of IE and NIE compared to usual care and compared to each other is presented in Table 3-12. For outcomes of pain, function, performance and QoL, both IE and NIE were consistently more effective than usual care. Furthermore, the estimated ES of IE versus NIE shows that IE is superior to NIE across all outcomes. These values were confirmed further by SUCRA scores, where the IE scores were clearly higher in all four outcomes. SUCRA scores for IE versus usual care ranged from 85 to 100 while the scores for NIE versus usual care ranged from 50 to 65.

Table 3-12. Summary of network meta-analysis results.

The table presents results of direct comparisons between individualised exercise (IE) versus usual care (UC) and between non-individualised exercise (NIE) versus UC and indirect comparison between IE versus NIE. The table shows the Surface Under the Cumulative Ranking Curve (SUCRA) scores of direct comparisons.

Outcome	Type of exercise	ES	95% CI	SUCRA
Pain	IE vs UC	0.96	0.47, 1.4	94.20
	NIE vs UC	0.62	0.45, 0.79	55.70
	IE vs NIE	0.33	-0.17, 0.84	
Function	IE vs UC	1.17	0.63, 1.71	100
	NIE vs UC	0.56	0.36, 0.75	50.0
	IE vs NIE	-0.60	-1.18, -0.03	
Performance	IE vs UC	1.39	0.72, 2.07	99.60
	NIE vs UC	0.53	0.37, 0.69	50.40
	IE vs NIE	-0.86	-1.56, -0.16	
QoL	IE vs UC	1.33	0.69, 1.96	85.30
	NIE vs UC	1.15	0.96, 1.35	64.70
	IE vs NIE	0.17	-0.83, 0.49	

3.6.3 Ranking probability

The probability of ranking explains the probability of each intervention to be either best, second or worst among the other interventions in the comparison. IE was ranked as the best intervention among the three interventions included in this study for all outcomes. IE ranked best with a score of 88.5% for pain, 98.2% for function, 99.2% for performance and 70.6% for QoL. This meant that IE was highly likely to be better than NIE and usual care in all outcomes with the least probability in QoL outcomes. Usual care was 100% worst in all outcomes. All ranking details are shown in Table 3-13 below.

Table 3-13. Ranking probability of included interventions for each outcome

Outcome	Rank	IE (%)	NIE (%)	UC (%)
Pain	Best	88.5	11.5	0.0
	Second	11.5	88.5	0.0
	Worst	0.0	0.0	100
Function	Best	98.2	1.8	0.0
	Second	1.8	98.2	0.0
	Worst	0.0	0.0	100
Performance	Best	99.2	0.8	0.0
	Second	0.8	99.2	0.0
	Worst	0.0	0.0	100
QoL	Best	70.6	29.4	0.0
	Second	29.4	70.6	0.0
	Worst	0.0	0.0	100

ES= Effect size IE= Individualised Exercise. NIE= Non-Individualised Exercise. UC= usual care. QoL= Quality of Life. CI = Confidence interval. SUCRA= the Surface Under the Cumulative Ranking Curve.

3.6.4 Sensitivity analysis

The NMA analysis was conducted with removal of the one study (Villadsen et al., 2013). The NMA sensitivity analysis was done on pain outcomes. IE is still significantly better than usual care (ES: 0.51, 95% CI 0.12, 0.89). However, comparing IE to NIE directly shows no significant difference as 95% CI crosses the no effect line (ES: 0.09, 95% CI -0.31, 0.49) (Table 3-14).

Table 3-14. Sensitivity analysis of pain outcomes' network meta-analysis results.

Outcome	Type of exercise	ES	95% CI	SUCRA
Pain	IE vs UC	0.51	0.12, 0.89	67.40
	NIE vs UC	0.62	0.45, 0.79	82.30
	IE vs NIE	0.09	-0.31, 0.49	

ES= Effect size. IE= Individualised Exercise. NIE= Non-Individualised Exercise. UC= usual care. QoL= Quality of Life

3.7 Discussion

3.7.1 Main findings

This study is part of the development process of an IE intervention. The review results help in identifying the current evidence supporting the use of IE for people with OA and the methods used to individualise exercise in previous studies. Identifying evidence and exploring the literature related to the topic are important steps to start developing an intervention according to the MRC framework.

This is the first systematic review to examine IE interventions for hip and knee OA. The search identified 17 trials that met the inclusion criteria. Data from eight trials were used in the CMA to assess the efficacy of IE compared to usual care. Overall, IE was significantly better than usual care for outcomes of pain (ES 1.00, 95% CI 0.35, 1.65) and function (ES 1.23, 95% CI 0.46, 2.01). However, for performance and QoL outcomes, ES was high but overall, the 95% CI crossed the line of no effect (performance ES 1.37, 95% CI -0.21, 2.95 and QoL ES 1.01, 95% CI -0.30, 2.32) meaning that there was no significant difference between IE and usual care for these outcomes. For NIE versus usual care, a total of 70 trials were identified for inclusion. Pooled ESs for NIE were also significantly better than usual care for all outcomes but were lower than those observed for IE, specifically: pain (ES 0.58, 95% CI 0.46, 0.71); function (ES 0.53, 95% CI 0.40, 0.65); performance (ES 0.52, 95%

CI 0.39, 0.64); and quality of life (ES 0.33, 95%CI 0.17, 0.49). The ES for IE was higher than that for NIE for pain and function outcomes, however for performance and QoL outcomes there was no significant difference.

The NMA was conducted to allow an indirect comparison between IE and NIE using the common comparator of usual care. The findings of this analysis were consistent with the CMA findings demonstrating that IE had larger effects over NIE across all included outcomes when compared to usual care. The largest effects sizes were observed for performance 1.39 (95% CI 0.72 - 2.07), followed by QoL 1.33 (0.69 - 1.96), function 1.17 (95% CI 0.63 - 1.71) and pain 0.96 (95% CI -0.47 - 1.4). For QoL and performance outcomes, the difference between IE and NIE ES was not statistically significant as the confidence intervals overlap. However, the SUCRA probability ranking, which is a unique comparison scale for NMA, shows that IE was the most effective intervention, followed by NIE and then usual care (Table 3-13).

The CMA results for IE studies showed a considerable level of heterogeneity with I^2 ranging from 95% to 97%. The heterogeneity score for NIE studies was lower than for IE, ranging from 72% to 75%. This means that the level of heterogeneity in the IE group is considerable, thus there is a good chance that the actual ESs of IE interventions may be higher or lower than those found in this study. It should be noted that this

high heterogeneity could be attributed to one outlying study (Villadsen et al., 2013). This study showed a significantly higher SMD than the average of the other studies (Villadsen et al., 2013). The results of that study showed significant improvement in all outcomes, the SMDs being pain 4.78, function 5.50, performance 2.99, and QoL 2.22. It was one of the largest included studies, and thus a “small study effect” would seem an unlikely explanation for these higher results. However, this study, which was compared to education alone, used a combined education and neuromuscular exercise programme, in which the exercise was individualised based on patient performance. This was the only study to have a dominant educational component and it may be that there was a positive (multiplicative) interaction between these two core interventions.

Therefore, a sensitivity analyses for both CMA and NMA was conducted with removal of the study by Villadsen et al. (2013). This has resulted in a significant drop in heterogeneity level, as well as lower ES for pain outcomes in IE studies. However, the effect of IE is still significantly better than usual care based on sensitivity CMA result, while the NMA sensitivity analysis showed no significant difference between IE and NIE.

Moreover, the I^2 of CMA of NIE studies versus usual care also shows a substantial level of heterogeneity, meaning that the results of both arms of the comparisons are subjected to high heterogeneity. A high level of

heterogeneity is a common issue in all exercise studies in OA (Bartholdy et al., 2017, Smith et al., 2012, Goh, 2018). The range of potential sources of heterogeneity in exercise studies includes wide variation in baseline characteristics of participants in different studies and variations in exercise types, settings, duration and frequency.

One of the aims of this study was to identify the ways in which exercise was individualised in the current literature. This will enable a better understanding of how exercise is currently being individualised and will help to structure an optimised individualisation method. The most common method reported for individualising exercise was performance-based progress, which was reported in three out of 16 trials, and individualisation based on severity of symptoms, specifically pain, which was used in three out of 16 studies (Foroughi et al., 2011, Allen et al., 2018a, Skou et al., 2015).

Individualisation based on participant performance essentially means progressing the intensity of the exercise to the highest possible level without affecting the quality of the exercise performed. Adaptations of exercise according to participant symptoms were conducted by either changing the type or the intensity of the exercise to ensure that the person could perform it with the minimal possible pain. However, none of the included studies detailed how pain was assessed during exercise.

Four other studies each used a different individualisation method. De Rooij et al. (2017) focused on the presence of comorbidities and provided three categories of exercise adaptations suitable for people with OA and comorbidities, OA with coronary disease and OA with a history of heart failure. The study by French et al. (2014b) individualised exercise based on assessment findings. However, that study did not provide sufficient details on what type of assessment was used and how exercise was modified during this process. Saccomanno et al. (2016) divided participants into three groups based on the compartment of the knee mostly affected by OA (varus knee, valgus knee and patellofemoral groups). Each group received a tailored exercise programme for their biomechanical needs. In the study by Segal et al. (2015) a physical assessment of strength, range of motion and flexibility was undertaken on each participant and the findings were combined with gait analysis to establish participant-specific goals. The exercise programme was designed based on these findings.

Eight studies were included in the review but did not enter the analysis stage because either the comparator was an active treatment, or it only used stratification of allocation or performed subgroup analysis rather than individualising the intervention for each group of participants. Five studies used stratification of allocation to group participants according to either

gender, age or BMI. However, in all these studies the exercise programme was the same for all groups and results did not specify whether any of the stratification groups responded to the intervention differently.

The quality of the intervention description was assessed using the TIDieR checklist. In general, the 16 studies included in this review provided details about the exercise programmes themselves in terms of types of exercise, frequency and duration. However, none of the identified studies covered all the items on the checklist. For example, exercise modification, which is one of the most important items needed to replicate the intervention, was one of the main problems encountered with IE description. Only one-third of the studies described how exercise was modified during the course of the study, while two-thirds did not refer to this point at all. Another important item for intervention description is the rationale or theory that explains why the intervention might work. Only 56% of studies explained the rationale for their intervention. Other items in the checklist are not strictly relevant to IE replication but were frequently missing, including the location of intervention prescription and any assessment of adherence to exercise. The average score of the studies in this review was 8.5 out of a total score of 12, with the lowest score being five (Cheing et al., 2002) and the highest 11 (de Rooij et al., 2017, Foroughi et al., 2011).

A risk of bias assessment showed a low overall risk of bias for IE studies. Around 90% of studies performed adequate randomisation of participants and the remaining studies stated that the study was randomised but did not provide a description of the randomisation process, so the risk of bias was considered unclear. Around 70% of the studies concealed the allocation of participants in the different arms of the study while the remaining studies had unclear allocation details. All of the studies reported the outcomes as specified prior to the trial and had homogenous baseline characteristics of their participants. Blinding was a consistent issue, and the results are thus subject to risk of bias. However, it is important to acknowledge that, in general, blinding of participants and clinicians to interventions such as exercise is not feasible. Blinding of assessors, however, is possible and this is important to minimise risk of bias within the studies. Unfortunately, only four studies performed assessor blinding (Allen et al., 2018b, de Rooij et al., 2017, Brismee et al., 2007, Henriksen et al., 2014a) while the majority of studies overlooked this process.

3.7.2 Findings in relation to previous research

The literature on IE for hip and knee OA management is scarce and this topic has not been previously systematically reviewed. The results of this review support the recommendations for patient-centred care (NICE, 2014). They are also in accordance with recommendations for individualised exercise in OA management (Fernandes et al., 2013).

However, this review highlighted a deficit in the literature for precisely how exercise was individualised in previous studies and how it should be individualised in practice.

One of the largest trials of IE for OA was carried out by Hay et al. (2018). Even though the study was included in the review however it was not part of the analyses part. This is because the CMA and NMA only included trials tha compared IE to no treatment or usual care (without active intervention). However, it is important to point out that this study has used two different ways to indivdualise exercise and both were applied on relatively large sample. One IE arm (Individually tailored exercise) included 176 particpants used assessments of miomechanical and physiological observations in addition to pain response to exercise as basis for indvidualisation. While the other IE arm (Targeted exercise adherence) inluded 163 participants used similar assessemtns but with addition of specific attention to adherence and adhrence barriers and potential facilitators. The study compared both IE arms to a usual physiotherapy intervention group. The comparator group received advice, educatio, Physio Tools exercise sheet and supervised physotherapy exercise programme (Hay et al., 2018).

The results of this trial showed no significant difference between the study groups in terms of pain and function outcomes after nine months and 18

months of treatment. Hence, in this trial, IE provided similar results to NIE for people with knee OA. However, adherence to intervention was higher throughout the study period in the targeted exercise adherence group than the other groups, indicating that giving specific consideration to adherence and discussing barriers and facilitators of exercise with participants individually can be effective in improving adherence to exercise.

IE is not only used for management of OA. Multiple studies have shown positive results from tailoring or individualising exercise in a number of conditions. A recent RCT reported significant improvements in participents with cardiovascular conditions by implementing an individualised aerobic exercise programme (Stavropoulos-Kalinoglou et al., 2013). The exercise programme in this study involved cycling, walking on treadmills and rowing. Indvidualised exercise in this study was based on the results of the exercise tolerence test (ETT), thus the intensity of the exercise wasdecided based upon how much the particpant could tolerate.

A number of trials have investigated the use of IE for people with musculoskeletal conditions. One study by Metsios et al. (2014) used a customised exercise programme (CEP) to improve self-efficacy and joint pain for elderly patients. The sample included 50 particpants with an average age of 69, mixing people with back pain, knee pain, osteoporosis and comorbidties in the same study. The CEP used a Japanese algorithm

developed specifcially to individualise exercise based on physical characteristics of individuals and estimated exercise based on age, sex, height, body weight, grip strength, walking velocity, bone mass, balance and intensity of joint pain (assessed by VAS). These data are used by computerised software to define which types of exercise, intensity and frequency should be performed by the participents (Japanese patent publication number, 2018–055626).

The CEP was used in the RCT by Metsios et al. (2014) as the intervention while the comparison group utilised a generalised exercise programme. The results showed that both arms of the trial had postivie outcomes in regards to pain and self-efficaccy but that there were no significant between-group differences. Given the small sample size and the large differences in the baseline characteristics of particpants, the CEP is worth exploring and developing further. Using such systematic and advanced ways to indvidualise exercise (if optimally developed) could be a turning point in how therapeutic exercise is prescribed.

Other studies have also compared IE directly to NIE. One RCT published in 2015 compared a form of IE to a generalised exercise programme for people with non-specific low back pain (NLBP) (Saner et al., 2015). The study included 106 particpants and found no significant difference between IE and NIE in pain outcomes (assessed by the graded chronic

pain scale (GCPS)) and function outcomes (assessed by the patient-specific functional scale (PSFS)). The IE programme in the study by Saner et al.(2015) focused on movement control impairment targeting specific functional actions. For example, they focused on core stability or hip stability in a specific functional task, such as sit-to-stand. The IE programme was tailored to improve movement control which in turn will improve functional ability. However, it should be noted that the IE programmes offered in this study did not seem significantly different from the NIE offered for the control group. Both prescribed programmes had almost the same structure, with minimal changes in the IE programmes. This raises the question of how much indivdualisation and tailoring is really needed before an exercise protocol can be considered IE, and not classic, standardised exercise with minimal tweaks. Currently the answer to this question is unclear and further research is required.

The results of the current review provide additional evidence that both IE and NIE forms of exercise are superior to usual care in OA management. This supports the results of previous research into OA and exercise (Fransen et al., 2015, Goh et al., 2019b). It also provides an indication that IE can be superior to NIE, which is in agreement with international recommendations. However, due to limitations in the available evidence, it cannot be definitively concluded that IE is better than NIE. Further, high quality, head-to-head RCTs are required.

One of the main findings of this study is that IE for OA is poorly described in the prevailing literature, leading to a generally poor ability to replicate the intervention. Poor description is a general issue with all exercise studies for OA and is not only limited to IE studies (Bartholdy et al., 2019). A recent descriptive analysis investigated this issue and concluded that many of the exercise studies that are used to inform international guidelines must have a good-quality description of their exercise programmes in order for them to be replicated in clinical practice (Bartholdy et al., 2019). Inadequate descriptions of interventions can result in serious uncertainty in clinical practice. IE is not an exception to this and quality of intervention description is critical for IE in order for it to be accurately replicated and developed.

3.7.3 Limitations

There are two major limitations of the results of this study. Firstly, the number of RCTs of IE for OA management is relatively small, and many include low numbers of participants and are of relatively short duration. Only 16 trials met the inclusion criteria and seven were included in the meta-analysis. Secondly, these studies utilised a variety of ways to individualise an exercise intervention, which makes it harder to draw conclusions about how best to individualise exercise for people with OA.

Having a small number of studies and inconsistency between findings makes the collective evidence weak.

To evaluate the treatment effects of any intervention it should ideally be compared against placebo/sham interventions (Harden et al., 2016). However, in exercise trials this is not always possible, and sham exercise as a comparator is arguably a form of intervention that is not entirely placebo. Usual care was therefore the most commonly used comparator for exercise studies in this review. However, estimating the effect of any intervention against usual care is also problematic, as usual care definitions vary among studies. Additionally, it should be considered that in the majority of controlled trials in which participants go through the procedures of a clinical trial, the results of an intervention may be different from real world practice, something that is known as the Hawthorne effect. In other words, the patients who are involved in a clinical trial may change their behaviour due to the fact that they are being studied (Cook, 1962). This may affect the participants psychologically and physically, which directly affects the results of the trial (Zuidgeest et al., 2017). This may have a particular effect on people undergoing IE, especially if they know that the intervention is tailored specifically for their needs, which may account for greater ES.

The research methodology also has several limitations. For example, the systematic review search was restricted to RCTs. Although this was necessary due to the nature of the methodology, it may have resulted in the preclusion of other informative studies of IE which were not RCTs. The search process and screening were thorough and carefully validated, however there is still a margin for human error that might have led to the oversight of some studies that should have been included.

CMA was used as the statistical method to analyse the overall results of the included studies. Subsequently, NMA methodology was used. NMA is a natural extension of CMA and is commonly used to compare interventions that are not compared head-to-head in clinical trials. However, these methodologies have some limitations, for example, the ES estimation can be influenced by the number of trials involved in the comparison arms (Li et al., 2011). For the current study, the overall sample size of IE (n= 991) studies is much smaller than the sample size of NIE (n= 6,072) studies. Therefore, although IE has a larger ES, it is less credible than the ES of NIE. Other factors can also influence NMA results, including heterogeneity of included trials, inconsistencies and potential sources of bias (Li et al., 2011).

3.8 Conclusion

The results of this review show that IE is effective in treating patients with hip and knee OA. IE showed greater ESs than usual care for pain, function, performance and quality of life outcomes. However, the available literature is relatively small and lacking in detail with respect to the ways that exercise was individualised. Further research is needed to investigate the individualisation and how to deliver IE for OA management. Future research should strictly consider high quality description of interventions and individualisation methods.

Chapter 4. Delphi study and stakeholders' meetings

4.1 Introduction

This chapter presents the process of determining consensus among international healthcare professionals and seeking the opinions of local stakeholders (rheumatologists, physiotherapists, and patients in Nottingham) on optimal methods to individualise exercise for OA patients.

4.2 Aims

1. To reach a consensus from an international panel of experts in OA and exercise prescription, from different healthcare professions, on the most important strategies for individualising exercise interventions for people with OA.
2. To gather the opinions of people with OA, physiotherapists and rheumatologists about strategies for individualising exercise for people with OA.

4.3 Delphi methods

The consensus process incorporated a three-step Delphi study. The study took place between March and May 2019. Table 4-1 provides an overview

of the Delphi process. Further details about each stage of the study are described under the relevant headings.

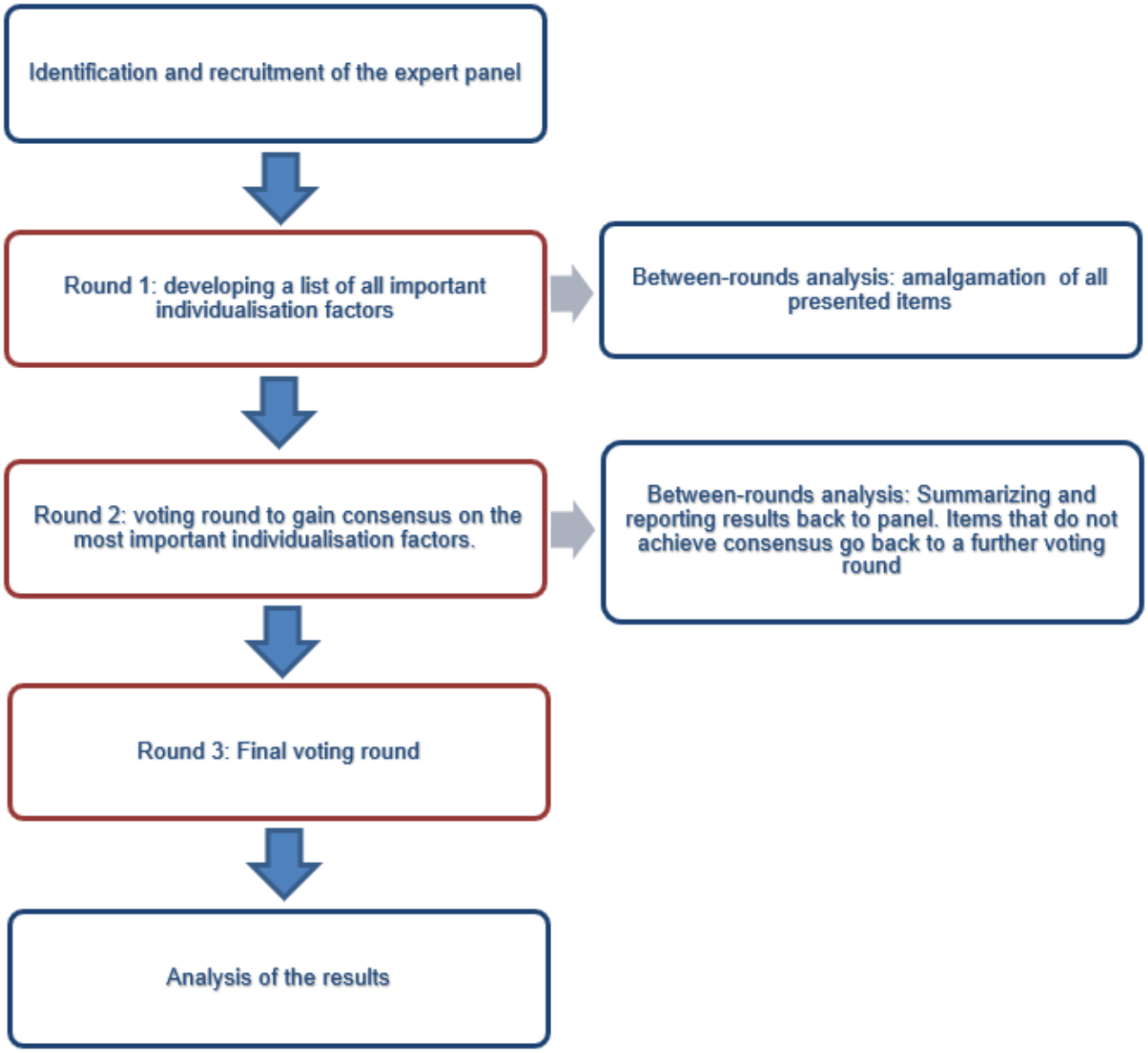


Figure 4-1. Overview of the study process.

4.3.1 Ethical considerations

The ethical committee in the Faculty of Medicine and Health Sciences were contacted to enquire if ethical approval was required for the study. The response was that the study did not require research ethics approval (Appendix 8: Delphi ethical approval).

4.3.2 Participant selection

There are no clear guidelines that suggest a particular panel size that is most appropriate for this type of study (Keeney et al., 2001). However, based on previous OA guideline development publications that have used Delphi methodology (Bannuru et al., 2019, Fernandes et al., 2013), the study team aimed to include a minimum of twenty experts in the field of OA care. The rationale being that heterogeneity is necessary to ensure high quality in performing the Delphi technique (Powell, 2003). Therefore, the study aimed to include a diverse group of experts that included rheumatologists, general practitioners and physiotherapists who are actively involved in academic and/or clinical practice. Academic expertise was identified by involvement in research, publications and development of international guidelines, while clinical expertise was identified by the years of practice that involved regular treatment of people with OA.

In order to identify experts in the field, a number of strategies were followed. First, the authorship of systematic reviews and international guidelines on exercise for OA was reviewed. Second, online profiles of potential participants were reviewed in specialised websites (e.g. Research Gate and Linked-In). Third, further experts were identified from supervisors' and peers' recommendations and professional networking.

Diversity was also considered with regards to locations of invitees. Identified experts were invited from multiple countries including England, Scotland, Australia, USA, Brazil, Denmark, Norway, Spain, Netherlands, and Malaysia.

Experts were invited via a formal email letter. This letter included a summary of the study and its rationale in the context of the whole research project, and a link to accept the invitation and to the first-round questionnaire (Appendix 9: Delphi invitation letter).

4.3.3 Survey procedure

The surveys were all prepared using Microsoft Forms software. This software offered a variety of features that facilitated the process of the study. Forms software enabled anonymity of voting, which is a central feature of the Delphi process. The software helps to summarise and

combine the results in graphs. Forms is considered a reliable and safe software that can be linked to emails with almost no risk to the privacy and security of participants.

The invitation email with the link to the first survey was sent to potential panel members on the 26th of March, 2019. Participants were given two weeks to complete the survey and were prompted to do so one week after the initial invitation letter. After the deadline, all responses were analysed, and second-round surveys were prepared and sent out to all participants. Again, a further two weeks' time was given, and a reminder was sent one week into the round. The same procedure was replicated for the third and last round.

4.3.3.1 *First round survey*

The first-round survey started by asking the participant to confirm willingness to participate in the study and some personal and professional details (name, profession, educational background, and current practice). Participants were then asked to list the ten most important factors or patient characteristics that they believed to be important for individualising exercise for people with knee and hip OA (Figure 4-2). At this stage, participants were not asked to rank the factors. The purpose of this round was to generate a comprehensive list of all possible individualisation factors.

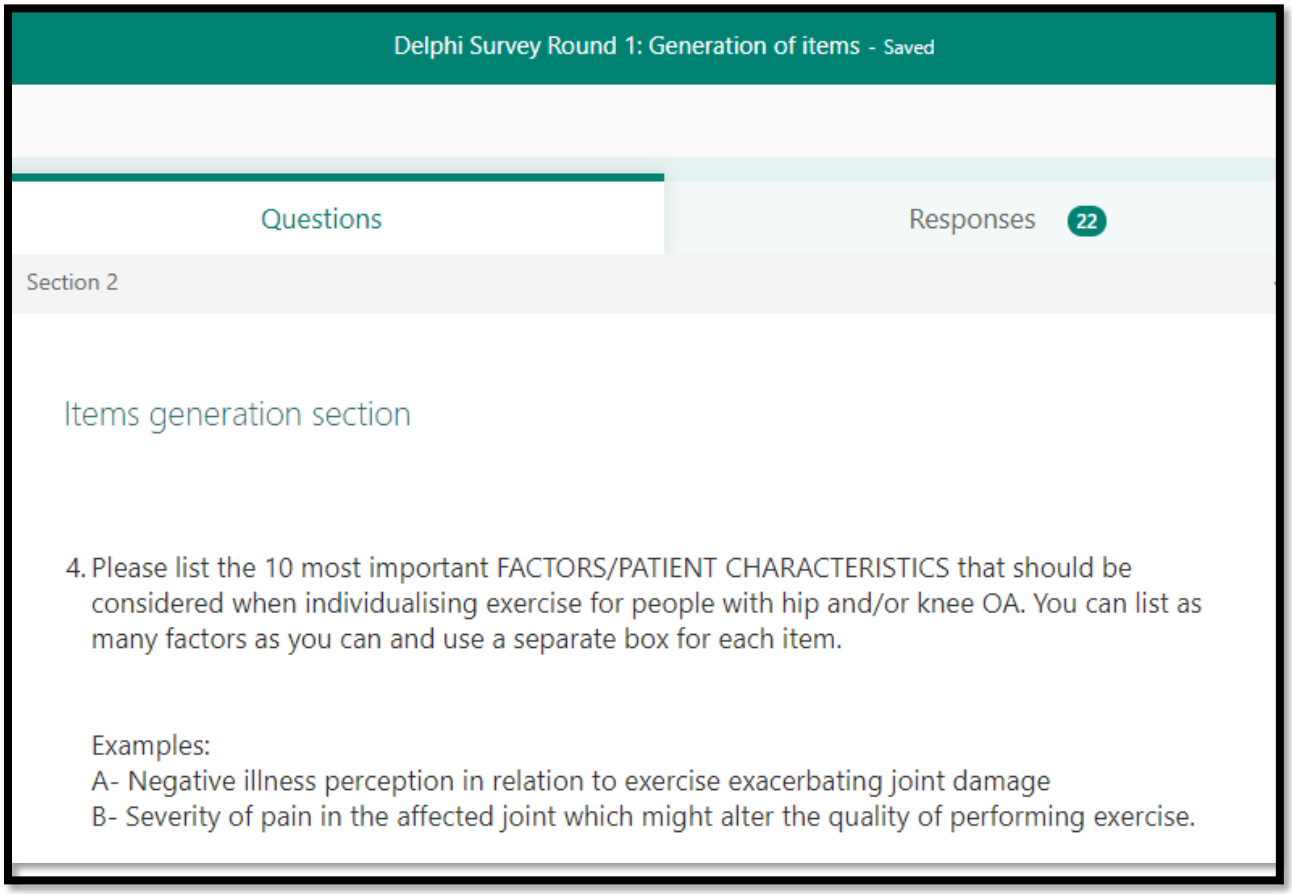


Figure 4-2. Delphi survey: Round 1

4.3.3.2 ***Second and third rounds voting surveys***

After completing the first round, a list of IE factors was generated. These factors were compiled and returned in a second email to the participants for voting. Participants were asked to answer Yes or No as to whether exercise should be tailored according to these factors. To simplify the process of filling out the survey, the items were grouped into similar domains such as patient characteristics and OA symptoms. An example of voting systems is presented in Figure 4-3. Participants were given 2 weeks to complete the second-round survey.

The returned results were analysed and items that did not achieve consensus were sent out for a third round of voting. The results of the previous round were summarised and reported to the participants and criteria for achieving consensus were clearly described. Participants were given 2 weeks to complete the third-round survey, again with a reminder one week into the round.

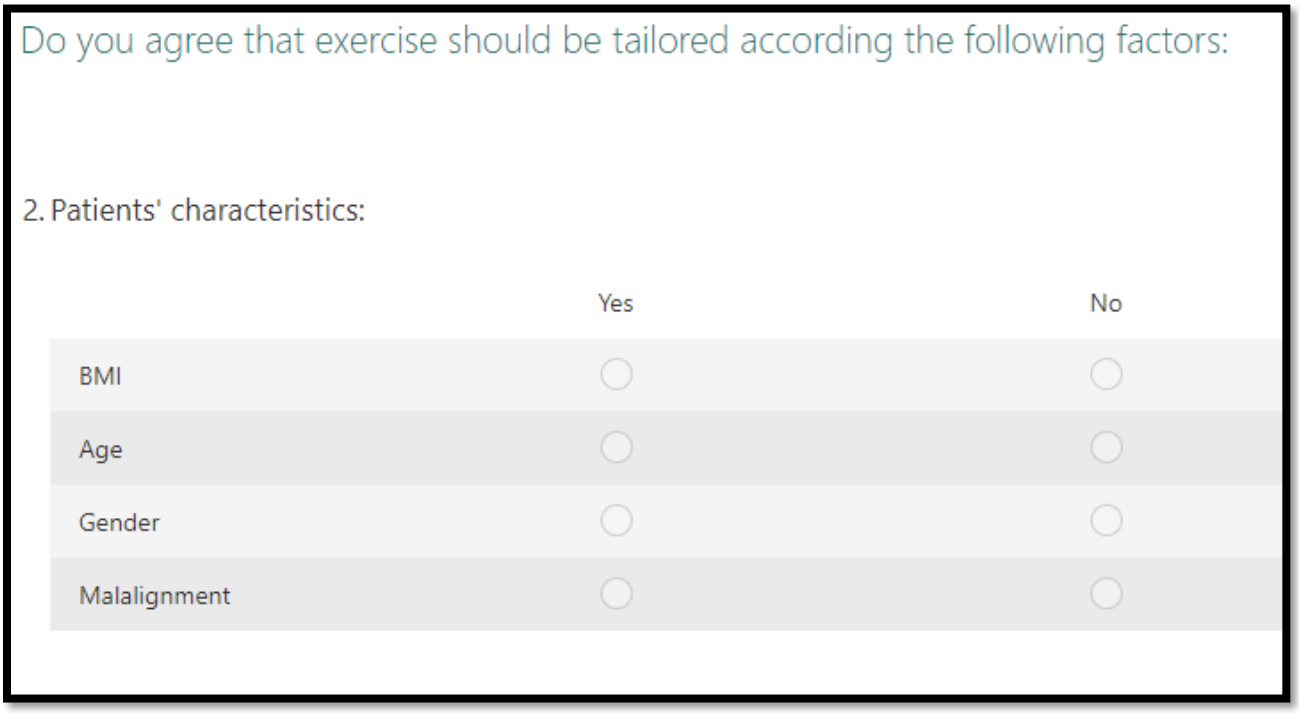


Figure 4-3. Delphi survey: round 2

4.3.4 Analysis between rounds

The Delphi technique is an iterative process where repeated communication and anonymised voting is used to refine participants'

opinions on topics of interest and achieve consensus. Therefore, it is necessary to analyse the responses between rounds. The items that did not achieve the pre-determined level of consensus either to accept or reject an item were sent out for further voting, together with the results of the previous round.

Percentage agreement was calculated for each item. These data were presented in charts for the participants to see in the next round.

4.3.4.1 *Determining consensus*

There are no acknowledged scores for determining consensus in Delphi studies and a variety of consensus measurements have been used in published literature. The pre-determined consensus level for this study (over 70% agreement) has been used in multiple past publications (Williams and Webb, 1994, Wells et al., 2014, Fernandes et al., 2013).

The statements that achieved between 70%-100% agreement were considered to have achieved consensus for inclusion as the most important items in IE. Statements that reached between 30%-69% agreement for inclusion failed to achieve consensus so were sent into the next voting round. Statements that attained 0%-29% agreement were considered to have achieved consensus to be excluded.

4.4 Delphi results

4.4.1 Participants

Invitations were sent to 52 potential panel members, 22 of whom agreed to participate. The rest either declined the invitation (6) or did not reply (14). All 22 participants completed all rounds in the study, giving a retention rate of 100%.

The expert panel included 12 physiotherapists, two rheumatologists and one general practitioner. The remaining seven participants selected “other” as their professional background. Most participants (13, i.e., 59%) worked in academic posts, three worked purely as clinicians and six worked in both academic and clinical practice. Experts from 7 different countries, representing 5 continents, participated in the study. The majority were from England (13) but the 9 others came from 6 other countries. (Table 4-1).

Table 4-1. Summary of participants characteristics

Professional background	Number
Physiotherapy	12
Rheumatology	2
Exercise science	2
Sports medicine	2
Exercise medicine researcher	1
General practice (Medicine)	1
Occupational therapy	1
Epidemiology	1
Current professional role	**Number**
Academic	13
Clinical academic	6
Clinician	3
Country	**Number**
England	13
Australia	4
Scotland	1
Brazil	1
Norway	1
Malaysia	1
USA	1

4.4.2 Delphi statements formulations (first round)

The 22 panel members generated a total of 37 different factors that they believed were important when individualising exercise for people with hip or knee OA. Among those factors, some were proposed several times by different members, for example: illness perception (20 times), pain severity (15 times) and presence of comorbidities (15 times). Others, such as duration of pain, gender and type of drug intake, were each proposed by just one member (Figure 4-4). However, all 37 factors were sent out in the next voting round to determine which ones achieved consensus for acceptance or rejection, and which needed to go into a further voting round.

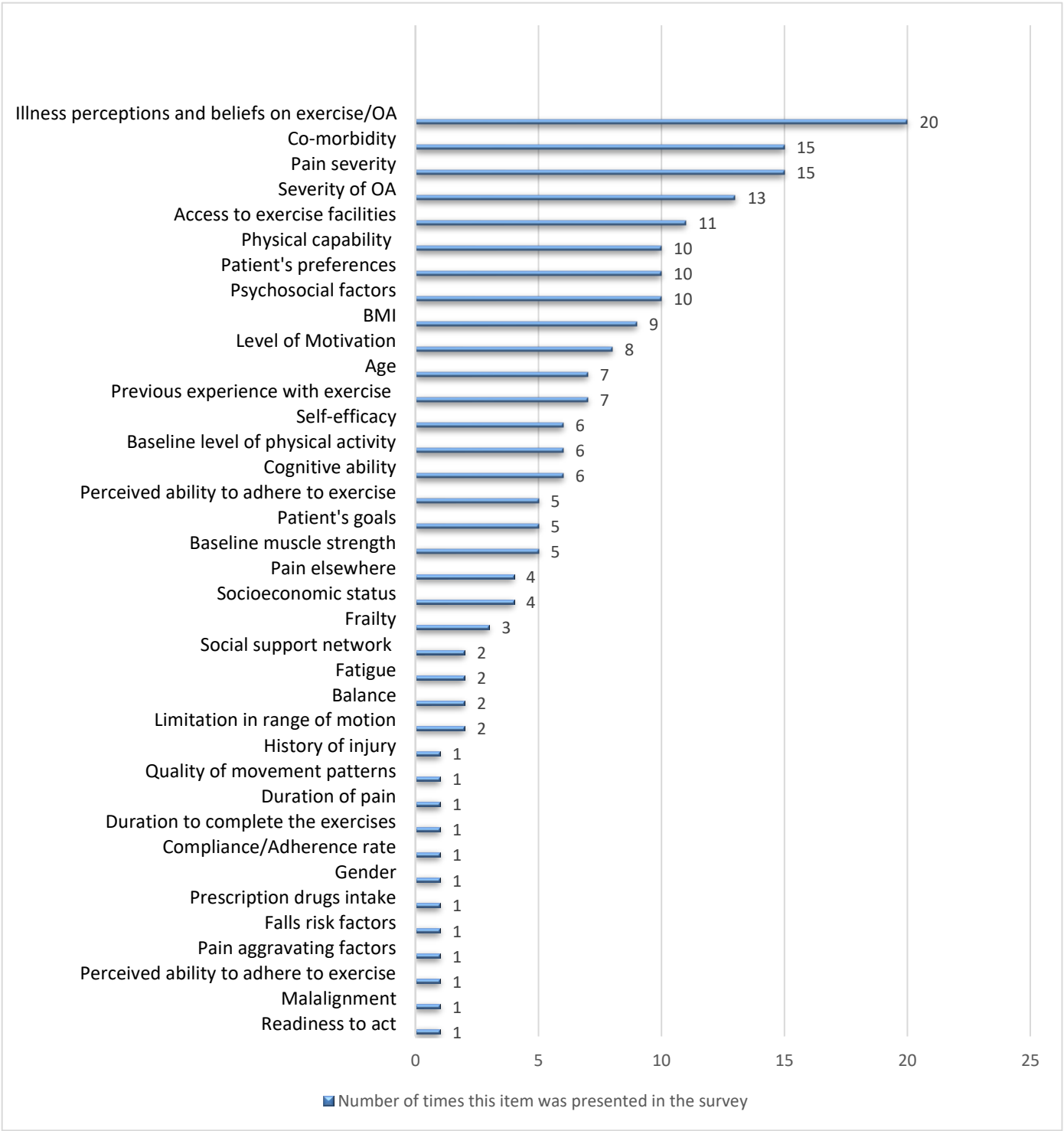


Figure 4-4. Full list of items generated in the first round with number of times each item was presented in the survey

BMI = Body Mass Index. OA = osteoarthritis.

4.4.3 Second round

In this round, all 22 members voted on the 37 items generated in the first round. A summary of the voting results is presented in Figure 4-5. Summary of Round 2 results and further details on level of consensus are shown in Table 4-2. Overall, 26 items achieved acceptance by more than 70% of the panel members (in blue), 9 items did not achieve consensus to either be rejected or accepted (in red), and only one item (gender) was rejected.

Table 4-2. Second round results.

Showing full list of items with voting percentages. Accepted items received a 'Yes' vote from at least 70% of voters. Rejected items received a 'No' vote from at least 71% of voters. Items that did not achieve consensus are those that had between 31% and 70%.

ACCEPTED (% agreement >70%)	
Factor	**Yes (%)**
Physical capability	22 (100)
Patient's goal	22 (100)
Pain severity	21 (95.4)
Pain aggravating factors	21 (95.4)
Frailty	21 (95.4)
Patient's preferences	21 (95.4)
Balance	21 (95.4)
Falls risk factors	20 (90.9)
Limitation in range of motion	20 (90.9)
Co-morbidity	20 (90.9)
Falls risk factors	20 (90.9)
Baseline level of physical activity	20 (90.9)
Baseline muscle strength	20 (90.9)
Cognitive ability	20 (90.9)
Level of Motivation	19 (86.3)
Compliance/Adherence rate	19 (86.3)
Perceived ability to adhere to exercise	19 (86.3)
Time constraints	19 (86.3)
Age	18 (81.8)
Pain elsewhere	18 (81.8)
BMI	17 (77.2)
Illness perceptions and beliefs on exercise/OA	17 (77.2)
Self-efficacy	17 (77.2)
Readiness to act	17 (77.2)

Fatigue	16 (72.7)
Psycho-social well-being	16 (72.7)
Social support network	16 (72.7)
NO CONSENSUS (% agreement >30% - 69%)	
Previous experience in performing exercise	15 (68.1)
Malalignment	12 (54.5)
History of injury	11 (50)
Socioeconomic status	11 (50)
Duration needed to perform exercise	10 (45.4)
Quality of movement patterns	10 (45.4)
Severity of OA	9 (40.9)
Prescription drugs intake	7 (31.8)
Duration of pain	7 (31.8)
REJECTED (% agreement 0-29%)	
Gender	4 (18.1)

BMI = Body Mass Index. OA = osteoarthritis.

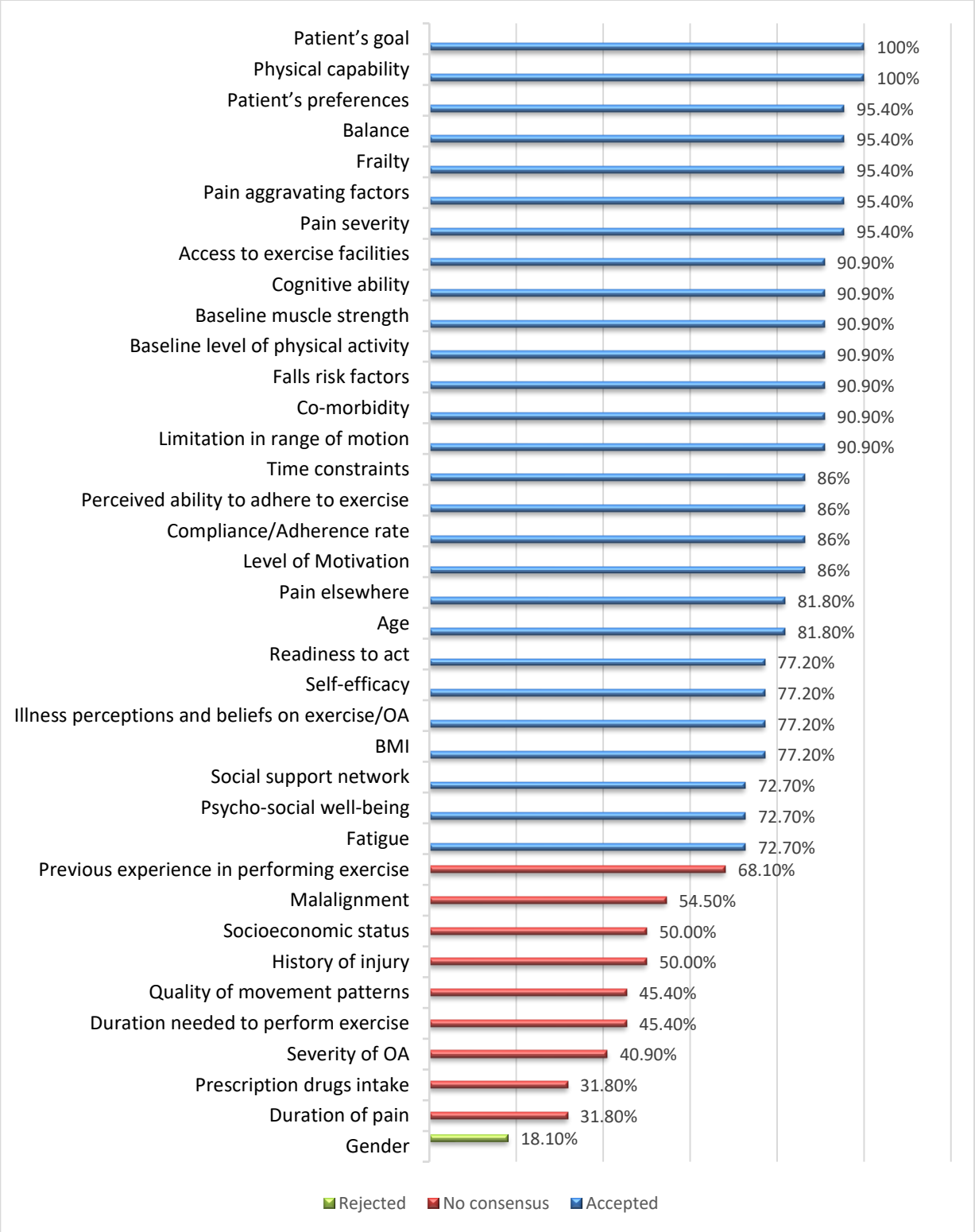


Figure 4-5. Summary of Round 2 results

BMI = Body Mass Index. OA = osteoarthritis.

4.4.4 Third round

In the third round, the nine remaining items were sent out for a further round of voting alongside a summary of the results from the previous round. This time, two of the nine items, specifically “duration needed to perform exercise” and “previous experience in performing exercise”, achieved >70% consensus for acceptance, while “prescription drugs intake” was rejected by more than 70% of the panel. This left six items that were neither accepted or rejected (Figure 4-6). Further details on the change of values from the second round to the third round are shown in Table 4-3.

Table 4-3. Third Round results

Showing full list of items with voting percentages. Accepted items received a 'Yes' vote from at least 71% of voters. Rejected items received a 'No' vote from at least 71% of voters. Items that did not achieve consensus are those that had between 31% and 70%.

Factor	Second round: Yes (%)	Third round: Yes (%)
ACCEPTED (% agreement >70%)		
Previous experience in performing exercise	15 (68.1)	16 (72.7)
Duration needed to perform exercise	10 (45.4)	16 (72.7)
NO CONSENSUS (% agreement >30% - 69%)		
Malalignment	12 (54.5)	11 (50)
Severity of OA	9 (40.9)	13 (59.1)
History of injury	11 (50)	11 (50)
Quality of movement patterns	10 (45.4)	14 (63.6)
Socioeconomic status	11 (50)	7 (31.8)
Duration of pain	7 (31.8)	10 (45.4)
REJECTED (% agreement 0-29%)		
Prescription drugs intake	7 (34.8)	2 (9.1)

OA = osteoarthritis.

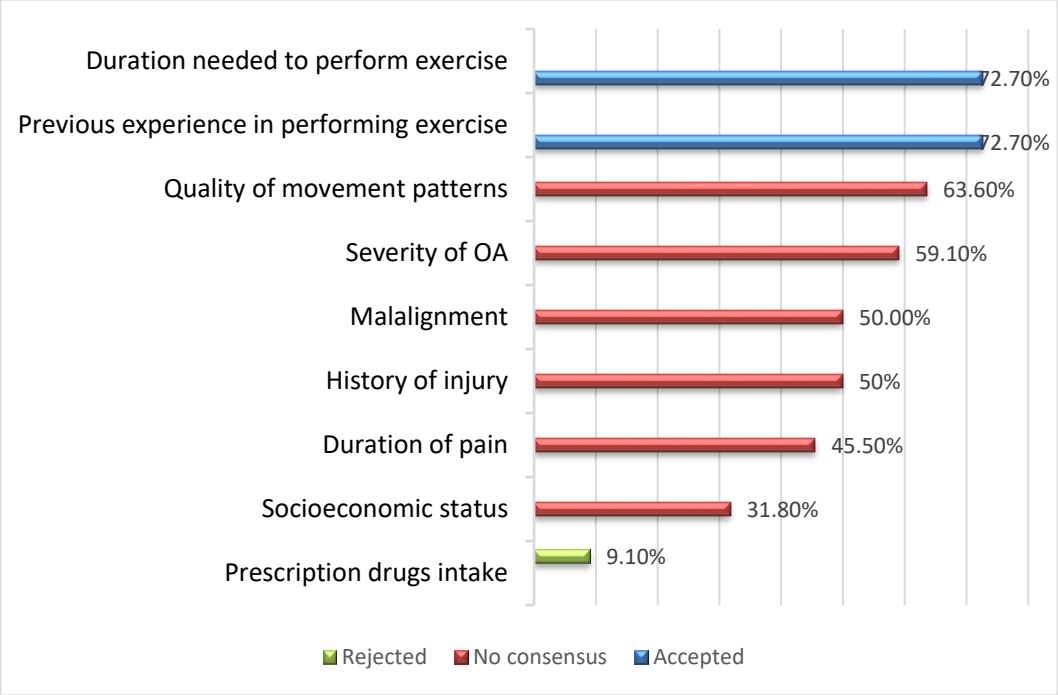


Figure 4-6. Summary of round 3 results

OA = osteoarthritis

4.4.5 Summary of Delphi consensus

The final list of results is presented in Figure 4-7. Twenty-eight items were accepted, two were rejected and six did not achieve consensus. The items that received the highest acceptance rates were patient's goals (100%), physical capability (100%), patient preferences (95.7%) and balance (95.7%). The lowest acceptance level was given to "prescription drug intake" (9.1%) during the third round, while the second lowest was gender (21.7%) during the second round.

All the items that were accepted were grouped into six categories (or themes).

1. Medical considerations
    i. Frailty
    ii. Co-morbidity
    iii. Age
    iv. BMI
2. OA Symptoms
    i. Pain severity
    ii. Pain elsewhere
    iii. Limitation in ROM
    iv. Pain aggravating factors
3. Baseline physical ability
    i. Physical capability

ii. Baseline physical activity

iii. Baseline muscle strength

iv. Balance

v. Falls risk factors

vi. Fatigue

vii. Previous exercise experience

4. Patient perspectives

    i. Illness perceptions

    ii. Preferences

    iii. Perceived ability to adhere to exercise

    iv. Patient goals

5. Psychological factors

    i. Cognitive ability

    ii. Level of motivation

    iii. Self-efficacy

    iv. Readiness to act

6. Social factors

    i. Social support network

    ii. Psychosocial well-being

    iii. Time constraints

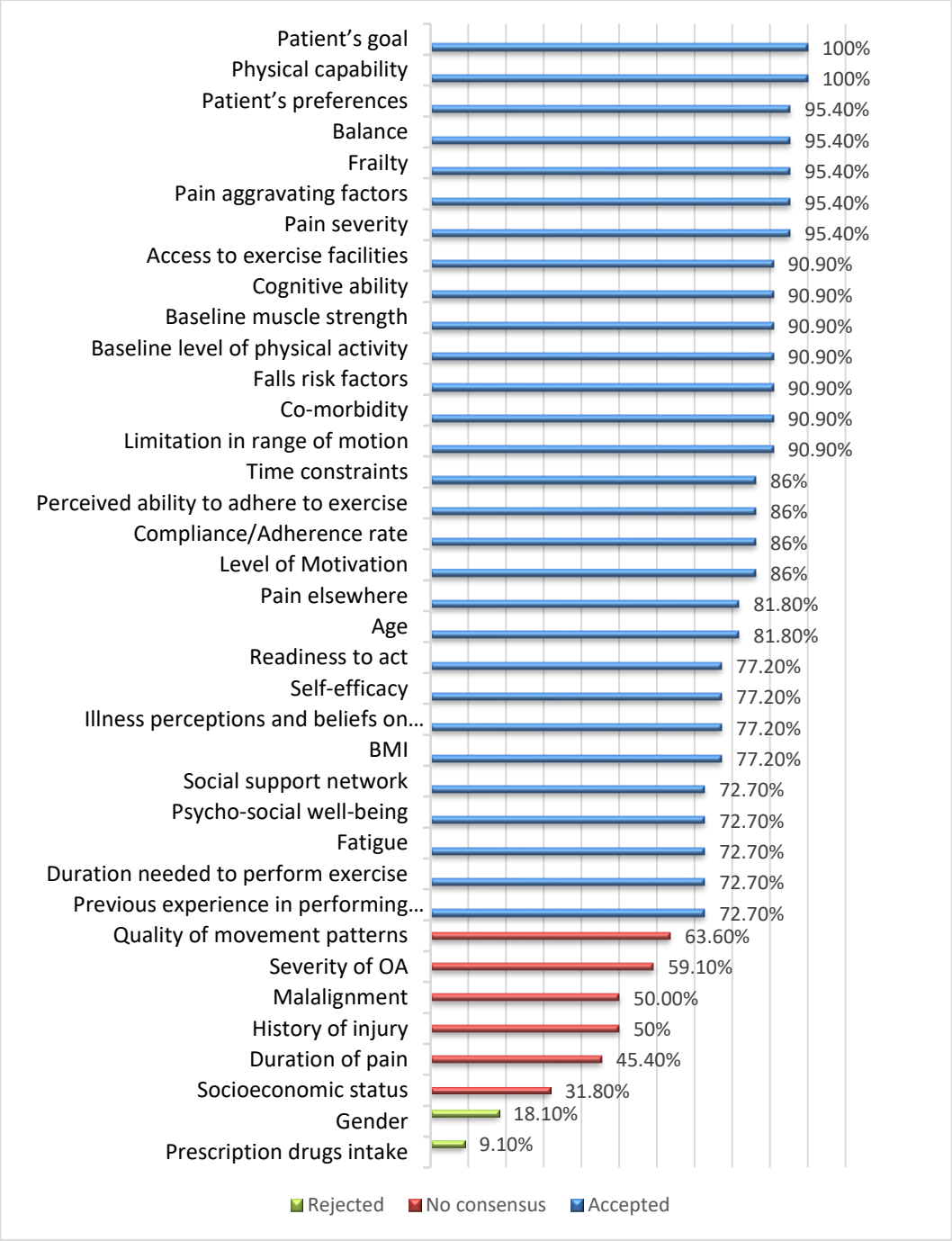


Figure 4-7. Final results summary

BMI = Body Mass Index. OA = osteoarthritis.

4.5 Stakeholders' meeting

4.5.1 Recruitment and identification of the stakeholders

To obtain a broad spectrum of opinions from people with potentially different perspectives, it was decided that the local stakeholder panel should include the following individuals:

- Physiotherapists who are frequently involved in managing people with OA.
- Practicing rheumatologists.
- Academics/researchers who are involved in research related to exercise for OA.
- People with OA (Public Patient Involvement [PPI]).

Identification of candidates for the professional panel (physiotherapists, rheumatologists and academics) was done through professional networking by the researcher and supervisors. For each field, several names were suggested and invited. Identification of candidates for the PPI panel was done through accessing the Knee Pain and Related Health in the Community study (KPIC) database (Fernandes et al., 2017b). All potential participants were contacted via email. An invitation letter was sent via email that included a brief about the PhD project and the purpose of the meeting.

4.5.2 Participants

Two separate meetings were held. The first was moderated by the PhD researcher (KY) and involved the primary supervisor (MH) as an observer, a physiotherapist, an Associate Professor in Physiotherapy and two patient representatives who regularly participate in PPI meetings. The meeting lasted 2.5 hours, including a short break, and took place in the Clinical Science Building in the City Hospital, Nottingham on Monday 12 August, 2019.

The second meeting involved the PhD researcher, one supervisor (AA) and 12 members of the rheumatology team (rheumatologists, trainees and nurse specialists). The meeting lasted 1.5 hours and took place in the Rheumatology Department at Queens Medical Centre (QMC) on Thursday 12 September, 2019.

4.5.3 Meeting format

At each meeting, a summary of the PhD project, the purpose of the meeting and a summary of the findings of the systematic review and Delphi study were presented. After the introduction, the main discussion started, which focused on how exercise should be individualised for people with OA.

Each of the six individualisation themes derived from the Delphi exercise were discussed in turn to facilitate discussion.

All participants were given time to express his/her opinion. After the discussion of each theme, a summary of opinions was written by the PhD student (KY) in the form of statements.

A summary of the meetings' highlights was written for each theme. Subsequently, the meeting summary was sent to the attendees to confirm the final list of statements.

4.5.4 Handling of data

Main opinions from each discussion topic were summarised into statements by the PhD student (KY). The statements were written in a secured computer monitored by university's IT team. During the meeting, the statements written were presented on screen for all participants to see. By the end of discussion, the participants can change or discuss any of the statements on screen. Additionally, after the meeting, a summary of the meeting including all the statements were sent to the participants to revise and make sure their ideas were captured accurately.

4.6 Meetings' results

The statements from both meetings were grouped and summarised in accordance with relevant theme of individualisation factors (Table 4-4). Full list of all opinions statements in each meeting is available in Appendix 10: Full list of stakeholders meetings .

Table 4-4. Summary of all statements in both stakeholders' meetings matched with relevant exercise individualisation themes generated in the Delphi study.

Themes from Delphi items	Opinion statements
Medical considerations • Frailty • Co-morbidity • Falls risk factors • Age • BMI	- Exercise should be performed within acceptable safety measures. - Balance exercise should be prescribed to people with a high risk of falls. - People with higher BMI should receive suitable exercise types including water-based exercise programmes. - Exercise should be tailored to be performed safely for vulnerable people and those with co-morbidities. - Presence of co-morbidity may impact each of the following: 1. The type and intensity of exercise programme. 2. Education about exercise benefits (exercise can be beneficial for OA and the co-morbidity as well). - The rheumatology team recommended giving considerable attention to frailty rather than age. It was suggested to use recognised measures for frailty for assessment.
OA symptoms • Pain severity • Pain elsewhere • Limitation in ROM • Pain aggravating factors	- Illness perception should be given a special consideration. - In the presence of musculoskeletal pain elsewhere, exercise can be prescribed to improve all affected areas not only OA joint. Mind-body exercises should be considered.

	- Exercise prescription should include alternatives for when the patient is having pain flare-ups.
Baseline physical ability • Physical capability • Baseline physical activity • Baseline muscle strength • Balance • Fatigue • Previous exercise experience	- Therapists should measure baseline abilities and set goals using objective measures (e.g. Pedometer and Dynamometer). - Subjective measures for tiredness and ability to exercise should be considered. - For those with fatigability issues, prescribe aerobic exercises to improve stamina. - Previous experience with exercise should be assessed as part of history-taking. - Exercise should start from the current ability of patient and progress gradually.
Patient perspectives • Illness perceptions • Preferences • Perceived ability to adhere to exercise • Patient's goals	- Education about OA and exercise benefits should be a core component of IE programmes. - Sessions should be a "two-way" learning process. Therapists should teach patients how to deal with pain and the differences between OA pain and normal exercise aches. Also, therapists should listen carefully to what patients say about their personal experience. - Expectations should be managed, and it should be explained that exercise may not completely eliminate pain and patients may still exercise even if pain is present within acceptable limits. - Patient preferences should be considered. Options for exercise can be provided and patients should choose what they consider to be enjoyable and achievable. Also,

	preferences regarding settings of exercise (in groups or alone, at the gym or at home). - Therapists and patients can structure individualised SMART (Specific, Measurable, Attainable, Relevant and Timely) goals.
Psychological factors • Cognitive ability • Level of motivation • Self-efficacy • Compliance • Readiness to act	- Set motivational strategies according to patient's preferences: 1. Role model. 2. Small achievable goals according to preferences. - Therapists should try to understand the social factors that affect the patient's adherence to exercise and barriers to adherence.
Social factors: • Social support network • Psychosocial well-being • Access to exercise facilities • Time constraints	- Therapists should be able to signpost patients to relevant exercising groups. - Special consideration should be given to known behavioural change strategies for exercise prescription according to patient's needs. - Therapists should try to understand the social factors that affect the patient's adherence with exercise.

The overall statements of both meetings can be succinctly summarised in the following statements:

- Safety of the patients: ensure that the prescribed exercises are safe for the patient.
- Presence of co-morbidities: therapists should carefully evaluate the presence of co-morbidities and modify the intervention accordingly.
- Patient's preferences: therapists should understand the main complaints and worries of the patient and provide relevant education and exercises.
- Psychological factors: therapists should understand the patient's perception of his/her illness and pain. Negative (or unhelpful) perspectives need to be discussed and addressed, and the fully informed patient should be involved in shared decision-making.
- Social factors: special consideration should be given to the social factors that may interfere with the patient's attitude towards participating in the exercise intervention. These social factors may include economic difficulties, lack of support and motivation from family and friends, and social responsibilities that prevent the patient from attending exercise facilities.

4.7 Discussion

4.7.1 Summary of findings

This study is an important stage of the development process of an IE intervention for people with hip and knee OA. The Delphi exercise alongside stakeholders' and PPI meetings helps identify the main factors for exercise individualisation for people with OA. Involving wider stakeholders in this process is considered among the core elements of interventions development. This process sits in the initial stage of developing and identifying the main factors of the IE intervention based on the MRC development process (Skivington et al., 2021b). However, stakeholders' involvement is also an important component of future evaluations of the intervention's development cycle.

The Delphi exercise identified 37 different individualisation factors that the panel suggested for IE prescription in OA management. After two voting rounds, the panel reached a consensus in accepting 28 factors as the most important. Two other factors were rejected by consensus and six factors did not reach an accepted agreement level. No further rounds were undertaken as the pre-planned number of rounds was completed.

The results of the Delphi exercise can help prioritise the list of individualisation factors according to the agreement level set. Thus, these factors were sub-grouped into five groups based on the agreement level

set, in which group 1 consisted of the most important factors with the highest agreement levels, and group 5 consisted of factors with the lowest agreement level (Table 4-5).

Table 4-5. Grouping of IE factors based on agreement levels in Delphi votes

Group	IE factor
Group 1 **(100% agreement)**	- Patient's goal - Physical capability
Group 2 **(95% agreement)**	- Patient's preferences - Balance - Frailty - Pain aggravating factors - Pain severity
Group 3 **(91% agreement)**	- Access to exercise facilities - Cognitive ability - Baseline muscle strength - Falls risk factors - Co-morbidity - Limitation in range of motion
Group 4 **(72-90% agreement)**	- Time constraints - Perceived ability to adhere to exercise - Compliance/Adherence rate - Level of Motivation - Pain elsewhere

	- Age - Readiness to act - Self-efficacy - Illness perceptions and beliefs on exercise/OA - BMI - Social support network - Psycho-social well-being - Fatigue - Duration needed to perform exercise - Previous experience in performing exercise

Group 1 has the two factors, which are the ones that achieved 100% agreement - patient goals and baseline physical capability. Group 2 included the five factors which received more than 95% agreement, namely patient preferences, balance, frailty, pain aggravating factors and pain severity. Taken together, these seven factors can be considered as the most important individualisation factors based on the Delphi results.

The purpose of grouping the IE factors into these groups was to facilitate prioritisation within the process of individualising exercise according to the identified factors. Thus, addressing IE factors in Group 2 is appropriate once the factors in Group 1 (inner ring) have been addressed.

Moreover, the stakeholders predominantly supported the findings of the Delphi. The discussions emphasised the importance of multiple factors that had high consensus levels such as patient preferences, their perceived goals, baseline physical capability and pain severity. The stakeholders also recommended giving special consideration to other factors such as illness perceptions, psychosocial well-being and safety of exercise programmes.

It is noteworthy that both the stakeholders and the Delphi panel highlighted the patient's perspectives as to his/her own goals and preferences, motivation, and self-efficacy as being at the centre for the individualisation process. Additionally, during both stakeholders' meetings, the person's illness perceptions and beliefs around OA and exercise therapy were considered a very important component in the IE prescription.

The person's baseline physical condition was also given paramount importance as physical capability was given a 100% agreement rate by the Delphi panel, and other factors such as baseline muscle strength and physical activity also scored high agreement levels. The stakeholders also viewed these factors as logical and important standards that should be assessed as part of usual practice for OA management.

4.7.2 Findings in relation to previous research

The findings of this study are unique since no previous study has attempted to identify important factors for individualising exercise for OA patients. However, some of the individualisation factors identified in this study have been utilised in clinical trials for OA management. For example, a study by Allen et al. (2018a) tailored an exercise intervention according to pain severity, functional ability and level of physical activity. The study included 224 participants. An internet-based IE was compared to a group on a waiting list with no intervention. In the IE group, patients were assigned to one of seven exercise difficulty levels based on assessments of pain, function, and baseline physical activity. Tailoring exercise based on these factors resulted in significant improvement in pain levels compared to the non-interventional control.

A study by French et al (2014a) utilised “physical assessment” to individualise their exercise protocol. This was a RCT that included a group of 131 participants divided into three experimental arms: one received an IE programme; one received a combined manual therapy and generalised exercise intervention; and the third group received usual care. The study showed that the IE group had significantly better improvement in pain and physical function that both the NIE and usual care groups. The factors of

exercise individualisation used in this were “physical assessment findings” focusing predominantly on muscle strength, though there was no clear description on how this influenced the exercise prescribed. The authors stated that the load of strengthening exercise progressed from low to high according to each individual’s ability. This further indicates the importance of the particular individualisation factors of baseline muscle strength and patient’s goals, which are among the factors that gained the agreement of the Delphi panel.

Conversely, some of the factors identified in the results of the current study have not been used previously to individualise exercise for OA and other conditions. For example, patient illness perceptions and perceived understanding of OA achieved a high level of consensus in the Delphi exercise, and were also considered very important in the stakeholders’ meetings. Addressing illness perceptions has been shown to have significant positive effects in management of OA and gout, showing good potential for optimizing the benefits and adherence to medical intervention (Botha-Scheepers et al., 2006, Dalbeth et al., 2011, Rees et al., 2013). However, this has not been considered in previous trials of IE in OA management. Additionally, although many psychological and social factors presented in this study are known to impact performance of and adherence to exercise (e.g. motivation and self-efficacy), none of those factors appear to have been taken into consideration in previous studies.

4.7.3 Strengths and limitations

Three Delphi rounds were completed with a 100% retention rate. Most statements achieved >70% consensus rate in the first voting round, which shows high levels of agreement between experts in this topic. Given the absence of robust evidence in this area, the >70% agreement should be taken as the best available evidence. However, it should be clear that this is not evidence of absolute unanimity. Therefore, the views of the experts' panel and stakeholders should guide the development of future research and clinical trials but not be taken as a definitive source of information or guidance. The views of the stakeholders strengthened the results of the Delphi exercise as their statements predominantly emphasised the importance of the factors generated by the Delphi panel.

There are strengths and limitations to all types of evidence, clinical trials, expert opinion/experience, and patient opinion, and it is only when all 3 concur on something that it can be considered a reliable evidential basis. This chapter attempted to gather both expert and patient opinions and experience on the most important factors to individualise exercise for people with OA. However, there is a need to synthesise this evidence with available literature on IE for OA and to perform clinical trials testing these findings.

One of the limitations of the results of this study is the absence of specific detail on how to individualise exercise intervention for each of the identified factors. The study helped identify 28 factors for individualisation that could be grouped into 6 themes. However, the details about how each of factors can be used to individualise exercise are limited. Additionally, the stakeholders' meetings did not provide sufficient details that helps prioritising the individualisation factors or giving more weighting to any factor over the others. However, the participants provided insightful opinions on how different factors might influence the process of individualising exercise from their own experience or knowledge.

The findings of this research are influenced by the perspectives of the participants. For example, all the items in the Delphi study were originally generated by the participants. Therefore, they may have been more inclined to accepting their own statements. Additionally, 59% (13) of the panel members were working solely in an academic context and only 13.6% (3) were full-time clinicians. Even though the academics could be considered "experts", being uninvolved in day-to-day interaction with OA patients may have influenced their views. In contrast, clinicians' views might have been overly affected by the system of the organisation they work in, their peers and the culture of their local clinical settings.

4.7.3.1 ***Stakeholders' involvement***

Seeking stakeholders' involvement in group meetings has some advantages and disadvantages. This kind of meeting is more efficient in terms of time and resources compared to one-on-one meetings (O'Haire et al., 2011a). Having people from multiple backgrounds provides rich and dynamic discussions that are usually informative. Also, the flexible nature of discussion helps to stimulate thinking and exploration of a wide range of perceptions and opinions (O'Haire et al., 2011a). However, in contrast to anonymised Delphi studies, these meetings are affected by power dynamics.

The effect of power dynamics on group meetings is established and explored in depth in previous social qualitative studies (Ayrton, 2019, Kessi et al., 2019). However, power dynamics in the context of health care research is known to have an impact on stakeholders' opinions, including professionals and the public/patients involved (Green and Johns, 2019). The participants in a face-to-face group meeting change their opinions or feel shy from expressing them because of perceptions they have about the other people attending the meeting. The attitude of meeting attendees can be affected by the perception they have about the status, position and expected views of the other members in the meeting (Nduna, 2020).

For example, in this particular meeting, the public and physiotherapists (practitioners and academics) attended the first meeting. In some cases, members of the public may have been affected by the opinions of the professional and may have avoided expressing their views that contrast with the views of the professionals. Additionally, power dynamics of some patients, public and professionals can affect the flow of the meetings. Some attendees tend to speak for a long time and dominate the discussion on certain topics. This can negatively affect the overall results of stakeholders' meetings.

The results of the stakeholders' meetings provided valuable input to the development process. This input is a list of opinion statements that are summarised from the dialogue and discussions on certain topics. However, the results lack specific details on how to prioritise individualisation factors. Having 28 interacting factors for individualisation is challenging, and there is a need to prioritise the important ones. Given that prioritisation was not the focus of the Delphi study, the stakeholders' meeting was a good chance to do it. However, this should be the focus of future work in developing and evaluating the intervention.

Additionally, future public and stakeholders' consultations invest more time and effort in recruitment and engagement. Recruitment should consider involving a wider spectrum of healthcare professionals and the public. A

higher number of invitations can be sent, aiming for a better response. Meetings can be separate for PPI and professionals to minimise the effect of power dynamics.

4.7.4 Interpretations and considerations for future research

The Delphi study relied on participants' views on developing the list of individualisation factors for voting. This process generated a long list of factors among which 28 items achieved over 70% consensus as an important factor of individualisation. This list shows how complex the process of delivering IE for OA management is, as some of these factors are related directly to the patient's physical state (e.g., strength and fitness) while others related more specifically to the OA symptoms, such as pain and ROM. Additionally, many psychological and social factors were also voted as equally important factors to consider in IE intervention.

It is also challenging for researchers to study and develop guidance for IE prescription. An extensive amount of research and clinical trials may be required to cover all potential variables that affect the outcomes of intervention. However, at present, it seems that a consensus or greater clarity in understanding how to optimally individualise exercise for patients with OA (and other chronic musculoskeletal conditions) has not been

realised. There is clearly a gap, therefore, in the literature in this regard and that is evident in the systematic review presented in Chapter 3.

This research warrants a need for future studies to identify detailed descriptions of how to individualise exercise based on identified factors. These details should, for example, be explicit about how different personal goals affect the choice of type and intensity of exercise and what type of exercise is better for patients with very low baseline physical capability.

There is also a need for further research to investigate how to prioritise the factors of individualisation and identify the key factors that need to be tested in clinical trials.

4.7.5 Conclusion

This Delphi exercise has provided a comprehensive list of the factors and characteristics that should be considered for IE intervention in the management of OA patients. Agreement was reached on 28 factors of individualisation. The accepted list of factors covered multiple aspects of the patients' condition including physical, psychological and social aspects. The Delphi study was followed by stakeholders' meetings that discussed the results in light of previous research. The meetings provided a list of valuable recommendations on how exercise should be

individualised. The results of the Delphi study and the stakeholders' meetings will inform the development of optimised IE intervention for OA management, which will be explained in further detail in the next chapter.

Chapter 5. Synthesis of the research evidence and the construction of the individualised exercise programme

5.1 Medical Research Council framework

The proposed intervention was developed over a 3-year process. Information was gathered from multiple sources including: the authors' core knowledge and clinical experience, a systematic review with CMA and NMA, consensus among experts in the field through a Delphi exercise and stakeholder meetings which included physiotherapists and people with OA. The process of intervention development was also undertaken in accordance with the MRC guidelines for developing and evaluating complex interventions (Skivington et al., 2021b).

Developing such complex interventions is ideally done in a continuous cycle of multiple phases, including identifying/developing the intervention, testing the feasibility of the intervention, evaluating the intervention, and implementing the intervention in practice (Figure 5-1). This cycle is continuous but not necessarily linear, as the information obtained at any stage can feed back to the previous stage or inform the progress of the next stage.

The current study covers the first phase of the development process, which is developing the intervention. The process of developing an optimised IE intervention involved multiple fundamental components, including evidence, theory, and modelling. Table 5-1 elucidates the structure of this process.

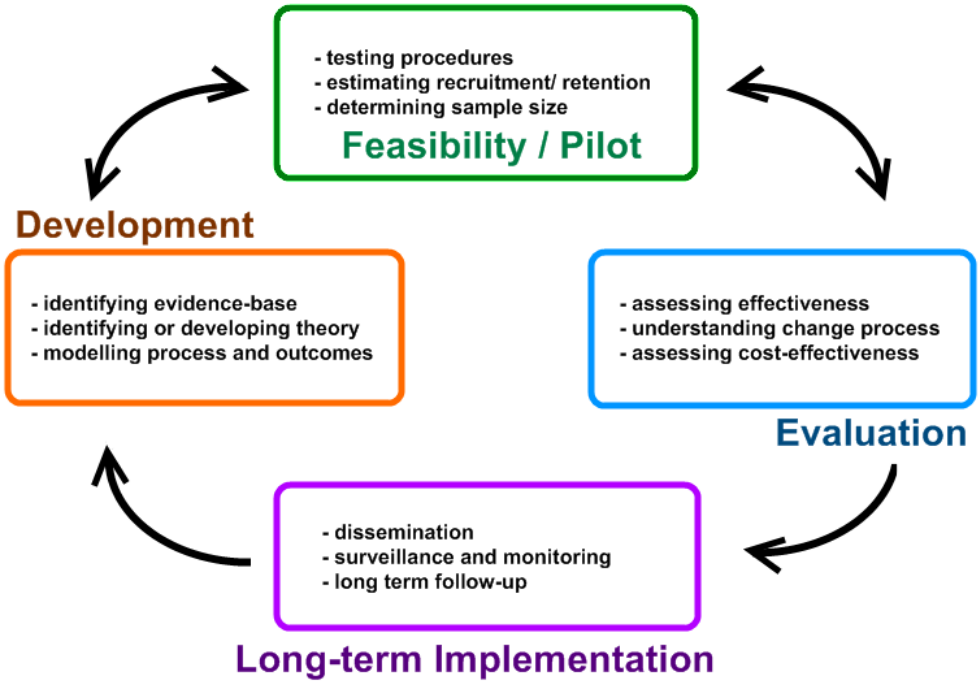


Figure 5-1 The cycle of intervention development process

Table 5-1. Summary of intervention development process

Stage of development process	Research activity undertaken	Relevance to development process
Research evidence	• Systematic review - Conventional meta-analysis - Network meta-analysis	• Systematically reviewing all studies that tested IE for knee or hip OA management. • Reporting the methods used for individualisation. • Evaluating the quality of the evidence. • Evaluating the quality of reporting the intervention. • Comparing the effectiveness of IE and NIE versus usual care. • Comparing the efficacy of IE versus NIE.
Clinical expertise and stakeholders	• Expert consensus: Delphi study • Stakeholders' meetings	• Identifying all important factors related to IE prescription from the perspectives of clinical and academic experts in exercise and OA. • Putting the Delphi results and results of previous studies into context by meeting various stakeholders: physiotherapists, rheumatologists and patients. • Patients' perspectives were gathered in form of public patient involvement (PPI) as part of stakeholders' meeting.
Modelling	• Core knowledge and experience of study group	• Guiding and advising the direction of the research based on experience from previous research and clinical practice. • Advising on the feasibility of what can be tested within the current research project. • Iterative process in planning the details of the intervention for the acceptability study.
Synthesis and testing	• Synthesis of data to develop the Intervention • Acceptability study protocol	• Developing the protocol for the study represents the synthesis process, where all the evidence, theories and core knowledge come together into an IE programme to be tested.

	• The study aims to test patient satisfaction and adherence and the feasibility of conducting a large-scale trial.

OA= osteoarthritis. IE= Individualised exercise. NIE= Non-individualised exercise.

5.2 Core elements of developing IE intervention

Developing complex interventions to be applicable in real-world practice, we need to shift our focus from investigating effectiveness in binary questions (i.e., effective versus not effective) to investigate in more depth the complexity of multiple elements of the intervention delivery and contexts. For developing an IE intervention, there is a need to understand how this intervention will be acceptable, implementable, cost-effective, scalable, and transferable across contexts (Skivington et al., 2021).

The MRC Framework has presented core elements of complex intervention development (Figure 5-2). This research project has provided data that covers a number of these elements while some uncertainties remain unanswered. The following will provide the relevant details of the core element of an optimised IE intervention for people with OA.

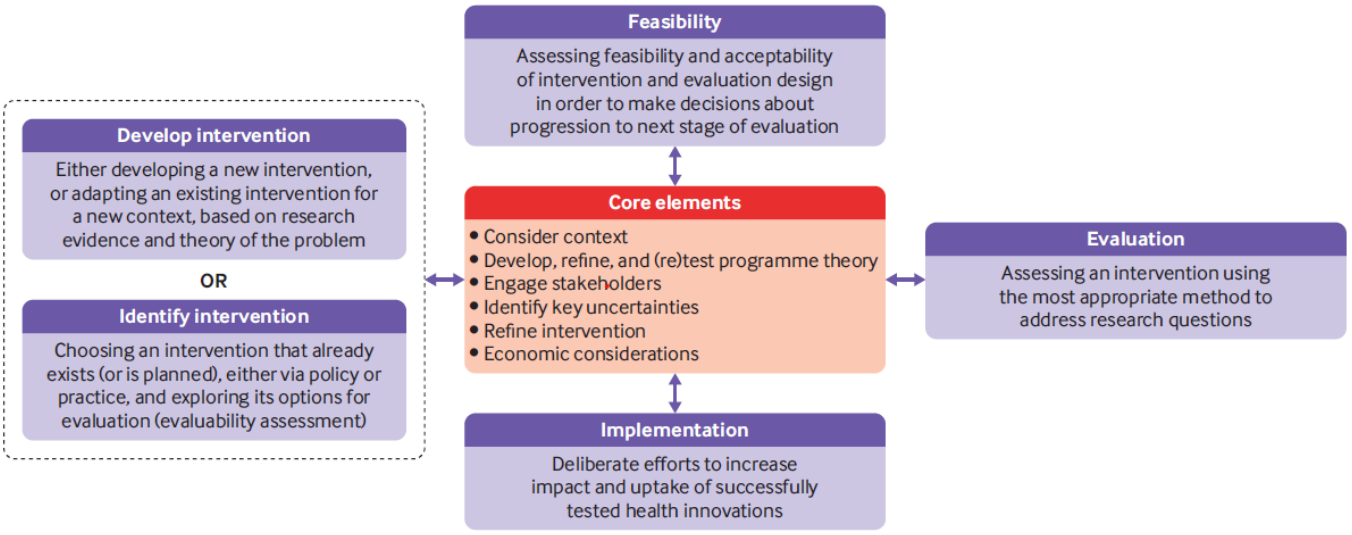


Figure 5-2 Core elements for intervention development (Skivington et al., 2021)

5.2.1 Context

The context of the delivery of exercise (or any complex intervention) can significantly affect the outcomes of this intervention. The context is the place where the intervention is delivered, the person providing the intervention, and cultural or social contexts. Any of those contextual factors affect the outcomes of the intervention. Therefore, it needs to be taken into consideration in the development process.

The context considered for an optimised IE intervention for people with OA involves that the treatment session is delivered by a qualified physiotherapist who is capable of assessing the patient based on a standard assessment protocol for all patients in addition to specific assessment for IE factors. The IE intervention involves multiple types of exercises, including strengthening, aerobic or flexibility (detailed in the

acceptability 6.2.6). The therapist teaches the person about the exercises suitable for them. This can be done verbally and by showing them how to do the exercises practically.

Examples can also be shown on printed materials or videos if needed. The intervention is delivered in a standard physiotherapy clinic or gym. All safety measures and essential equipment are provided. Sufficient time is allowed to teach the person with OA how to perform the exercises and what they need to do regularly. The cultural and social barriers to exercise should be discussed and taken into consideration. For example, if the person does not feel comfortable doing exercises in the gym, an alternative home exercise that serves the purpose can be prescribed.

This optimised IE intervention is not exclusive to people in the UK and can be generalised for use in any physiotherapy practice around the world. It can also be efficient from the economic perspective (see economic consideration 5.2.5).

5.2.2 Programme theory

The programme theory that explains how the intervention being developed can lead to desired outcomes is known as programme theory. A programme theory is a form of theory or model that explains how a complex intervention (e.g., IE) affects a chain of factors leading to the

desired outcome (Funnell and Rogers, 2011). This theory should ideally identify the key components of the intervention and the mechanisms in which the intervention might lead to desired effects (Funnell and Rogers, 2011, Skivington et al., 2021b). The theory can also identify the key uncertainties and relevance of the intervention to broader contexts (Lawless et al., 2018).

The programme theory of current IE intervention was developed during the course of the research. As information was gathered from the literature and from the results of the SR, Delphi and stakeholders' involvement, multiple important factors of IE intervention were identified. For example, some physical factors, such as baseline ability in terms of muscle strength and endurance, were identified. Other factors related to the psycho-social status of the person, such as self-efficacy, and motivation presence of social support network, were also seen as essential factors. Thus, the biopsychosocial model was considered a logical and holistic model to explain the underpinning mechanisms of this IE intervention (see underpinning theory 5.3).

Undertaking such a holistic approach in delivering an IE intervention implies that contextual factors are considered. For example, part of the biopsychosocial model is to consider psychological factors affecting the patients' adherence and use of goal setting as source motivation. Also,

considering the patient's social surroundings, for example, discussing if the person has family or friends to motivate them to exercise or do exercises together such as going for walks or gym. Therefore, the programme theory of IE interacts meaningfully with the context of delivery and this interaction can directly affect the overall outcomes of the intervention.

5.2.3 Stakeholders

Involving stakeholders in developing complex interventions is important to maximise the chance of having a positive impact on the intervention. The importance of involving stakeholders in different stages of intervention development was highlighted in the recent update of the MRC framework (Skivington et al., 2021a). Meaningful involvement of practitioners, patients and decision-makers was considered essential in all stages of research. Working together as a team can efficiently identify research questions, key uncertainties, programme theories, and prioritise different elements of research (Guise et al., 2013, Skivington et al., 2021a).

Additionally, considering the opinions of those targeted by the intervention and those involved in delivering the intervention helps identify key elements of the intervention from different viewpoints. Therefore, choosing the appropriate and relevant stakeholders is important to avoid having a narrow perspective of the intervention's efficiency (Skivington et al., 2021a, Greenhalgh et al., 2019).

Stakeholders' involvement is a key component of developing the IE intervention. They were involved in two stages of the development process and will be involved in future stages. A group of patients, clinicians and academics were involved in the Delphi study and stakeholders' meetings. Their input was key in identifying the main factor for the individualisation of exercise for people OA. Additionally, a PPI meeting was conducted as part of the modelling phase (see PPI section 5.4). However, due to time and resource restrictions, stakeholders' involvement was limited in developing and identifying research questions, programme theories and the modelling phase of the development process. This should be given specific consideration in future phases of the research.

Involving stakeholders can be done in multiple ways. An example of that is face-to-face meetings in groups (similar to what was done in this study) or in separate individual meetings. Additionally, stakeholders can be consulted by questionnaires, Delphi studies or other methods for written communication. Each method of involvement can offer a different type of input. The choice of method is ideally made depending on the phase of the development process and the type of information we are seeking to gather.

5.2.4 Uncertainties

In developing an intervention, key uncertainties related to the intervention's feasibility, effectiveness and context of delivery need to be identified. This can be done by reviewing the relevant literature, consulting the stakeholders, and developing a clear programme theory that explains how the intervention can lead to desired effects (Skivington et al., 2021a). Identifying new uncertainties can then result in framing additional research questions. Then the research is focused on finding answers to these questions and getting a better understanding of the intervention being developed. Nevertheless, complex interventions such as exercise have multiple interacting elements that create variable uncertainties and finding clear answers for them is a challenging process. In addition, even with highly clinical trials that provide clear estimates of outcomes, translating these results to diverse work settings is a complicated process (Skivington et al., 2021a). Thus, the developed interventions need to be continuously assessed and refined in development cycles to make sure they are being efficiently implemented in practice.

In developing an IE intervention, the main aims of this intervention were to improve the effectiveness of exercise intervention and improve adherence to it. However, many queries need to be answered in order to achieve these aims. Some of them were answered in this research project (to

some extent of certainty), while others remain unanswered. Those can be summarised as follows:

List of uncertainties:

- Is IE effective in improving outcomes of pain, function, performance, and quality of life in hip and knee OA patients?

  The answer based on SR results is yes. IE was found to be better than usual care in treating OA patients.

- Does IE provide a superior effect compared to NIE as an intervention for people with knee OA patients?

  The results of the NMA show that IE has a superior effect to NIE in treating people with OA. However, this is not conclusive evidence due high heterogeneity in IE studies. Therefore, this question warrants further investigation.

- What are the most important factors to be considered when individualising exercise for hip and knee OA patients?

  According to the SR findings, the IE factors varied in the included studies. There was no consistency; therefore, it remains unclear which individualisation factors are most important. The Delphi study succeeded in identifying an extensive list of IE factors that achieved consensus among a panel of experts. However, prioritising which factors are most important remains an unanswered query.

- Is applying an optimised IE on people with hip and knee OA feasible and efficient? Can the proposed IE intervention be translated to diverse clinical settings?

  This question can be answered by well-constructed acceptability and feasibility studies that investigate how acceptable IE is for practitioners and patients, what resources are required to deliver the intervention efficiently, and if it is cost-efficient. Additionally, stakeholders' involvement is essential in understanding these uncertainties from a diverse perspective. Stakeholders (including PPI) can be involved in designing the feasibility and large-scale trials and in developing the intervention.

5.2.5 Economic considerations

One of the main elements of intervention development is economic consideration. Evaluation of the economic efficiency of the intervention and the research methods are important elements of the development process. Researchers should investigate whether the resource and outcome consequences of the intervention on organisations, practitioners and patients are worth implementing the intervention or not (Skivington et al., 2021b). Additionally, it is important to consider the alternative approaches to minimise the cost of resources and consequences as a core component throughout the intervention development research (Skivington et al., 2021b).

Even though exercise is not considered and costly intervention in comparison to other medical care interventions (Miyamoto et al., 2019), it is still important to understand the cost-effectiveness of the IE. Especially in the current situation of economic crisis worldwide and the effects of covid on the global health care economy.

IE may not be very different from usual exercise therapy in terms of financial expenses. For health organisations, the change in the way exercise is delivered does not require longer treatment sessions than usual or any additional exercise equipment. Also, if the intervention achieves better adherence than usual exercise intervention, this will lead to making the patient less dependent on the health care system and less load on physiotherapy services. For people with OA, the majority of the exercises prescribed can be performed in a physiotherapy clinic, a gym or at home. In fact, flexibility and patient preferences are key components in the proposed individualisation process as they can lead potentially to sustainable adherence. However, these assumptions need to be investigated in depth in future studies. (e.g., feasibility study).

5.2.6 Intervention refinement

Evaluation and refinement of the intervention are essential elements of developing complex interventions. Refining the intervention is typically

done upon transition between different phases of the development process (Skivington et al., 2021a). Refining the intervention is done based on the data collected from the research progress (e.g., feasibility study). However, the refinement should be guided by the programme theory and stakeholders' involvement.

Evaluation of the IE development process will be done by analysing the findings of the acceptability study and consulting stakeholders in planning the next stage of the study (e.g., feasibility study or RCT). Additionally, refinement of the proposed IE and choice of IE factors are expected to be carried out based on the results of the acceptability study, in addition to input from the research and stakeholders' engagement. Furthermore, refinement and evaluation work should consider assessing the fidelity of intervention delivery. This is particularly problematic in clinical trials of exercise intervention as it can be difficult to tell if the results (positive or negative) are due to the intervention, poor delivery or lack of adherence (Broekhuizen et al., 2012).

Any change in the development process and/or the proposed IE intervention will be guided by the biopsychosocial theory aiming to achieve the main outcomes of the intervention, which are: improved outcomes and prolonged sustainable adherence.

5.3 Underpinning theory of an optimised individualised exercise intervention

Multiple mechanisms can explain why IE could provide positive outcomes for people with OA. These mechanisms can be explained from a biopsychosocial model point of view, as IE can have physiological, psychological and social effects that lead to improved outcomes (e.g., pain and function).

Overall, IE can theoretically improve a patient's outcomes because it offers an intervention that is focused exactly on what the person needs, in contrast to NIE. A patient-centred, tailored exercise programme will hypothetically achieve a better effect in improving symptoms as well as longer adherence through two interacting mechanisms, as explained in the following.

5.3.1 Physiological mechanisms

Individualising exercise based on a person's baseline physical abilities can be categorised as a biological mechanism. Individualising exercise based on baseline physical activity and muscle strength requires that the physical abilities of a person with OA are assessed first, then the exercise programme is designed to match the person's characteristics. Assessment of baseline abilities may include assessment of muscle strength, endurance, flexibility and overall level of physical activity. Testing muscle

performance can dictate the intensity, frequency and load to be prescribed for the patient. For example, a higher load with lower frequency can lead to improvement in muscle strength, while higher frequency with a lower load can lead to improvement in endurance (Williams et al., 2007). For exact details of weights, frequency and rate of progression, accredited international guidelines such as the American College of Sports Medicine (ACSM) can be followed (Liguori, 2020).

Physical activity can be assessed by simply asking the person about their daily routine and types of activities undertaken or by using specific questionnaires for physical activity assessment such as the International Physical Activity Questionnaire (IPAQ) (IPAQ-SF, 2002). These records can be compared to international standards of physical activity for the appropriate age group (WHO, 2011b). The therapist can then educate and guide the person to improve their physical activity level and provide suggested activities that match the person's preferences. In addition, some validated physical activity questionnaires can be used to assess and monitor levels of physical activity, for example the International Physical Activity Questionnaire (IPAQ) (IPAQ-SF, 2002).

The hypothesised responses to this intervention from a physiological perspective can be summarised as follows: stronger muscles, better

movement control, better balance, better joint mobility and less pressure on the joint surface. These responses will eventually lead to a reduction in pain and an improvement in function.

In general, exercise has multiple biomechanical benefits for the joint. For example, as regards the knee, studies have shown that improving the strength of the quadriceps through exercise can decrease weight-bearing pressure on the knee joint surface, which is one way to reduce pain (Muraki et al., 2015, Alkhawajah and Alshami, 2019). Additionally, OA causes decreased mobility in a joint, which affects its functional ability. For example, in the early stages of knee joint OA, a limited range of motion appears in many cases (Chaudhari et al., 2019), principally in the end range of flexion or extension, mainly due to pain or biomechanical changes within the joint. Different types of exercise, such as strengthening and flexibility exercises, can be prescribed to improve joint mobility. However, identifying the main mechanical problem by appropriate assessment and choosing an appropriate exercise for the specific individualised abnormality are important to achieve the desired outcomes.

Individualising exercise to the specific physical needs of a person is a common practice used by physiotherapists. For example, therapists assess the physical abilities of the person and then prescribe exercises based on what they think is lacking. However, there is no specific

guidance to show the details of exactly which exercise should be used, with different variations in regard to physical abilities. Typically, exercise is individualised based on the therapist's experience.

5.3.2 Psychological and social mechanisms

Additionally, IE can have psychological mechanisms that can lead to improved outcomes, specifically pain and adherence to exercise. psychological and social factors can reduce pain levels by affecting the central sensitisation aspect of chronic pain. Additionally, improving confidence, self-efficacy and motivation can lead to better adherence to exercise.

Therefore, an IE programme should consider factors such as setting goals, as each person's functional goals are a significant component of the individualisation process. For example, if a person with OA aims to get back to practising sports, this would require different exercise goals and a different regimen to a person whose primary objective is simply to resume basic activities of daily living. It is hypothesised that setting goals can help motivate a person to exercise and may improve their adherence to the prescribed exercise.

This hypothesis is also supported by the literature, as setting clear goals for a treatment is known to have a positive psychological impact on

patients, which can help improve adherence to the intervention and therefore the outcomes (Galluci, 1995, Wilson and Brookfield, 2009). The relationship between setting goals and improving adherence has been explained by the theory of psychological success cycles presented by Hall et al. (1977). More recently, Swann et al. (2021) reviewed the published literature on the effects of goal-setting on physical activity and exercise in the general population. Their study highlighted that appropriate goal setting is important for adherence and engagement with exercise. However, the authors also warned that setting unrealistic goals can have a negative impact (e.g., discouragement) on the person's attitude to exercise.

Additionally, a person's illness perception and perception towards exercise can have a serious impact on their psychological state. The way a person understands their condition can cause fear of movement, catastrophising of symptoms and other negative psychological effects that can directly affect their symptoms and adherence with an intervention.

Illness and intervention perceptions were linked to adherence to intervention in several studies. A cross-sectional study considering 157 participants investigated the link between illness/intervention perceptions and adherence to exercise, diet and medication in diabetic patients. The study assessed illness perceptions using the Brief Illness Perception

Questionnaire (Broadbent et al., 2006) and concluded that the majority of those with a good understanding of their illness and the importance of a healthy diet and exercise were more committed to interventions (Broadbent et al., 2011). Additionally, two observational studies have reported that illness perceptions are linked to adherence and compliance with medical interventions in patients recovering from breast cancer (Lan et al., 2019) and coronary heart conditions (Mosleh and Almalik, 2016).

Negative perceptions of OA, such as it as an inevitable wear-and-tear condition that inevitably progresses to surgery and about which very little can be done, are very prevalent in the general population (which includes people with OA) (Hill et al., 2011, Darlow et al., 2018). Few studies have explored the role of illness perception in arthritis management. A longitudinal cohort study by Bijsterbosch et al. (2009) investigated the association between illness perception and progression of symptoms and disability in people with OA. The study measured the illness perception of 241 participants at baseline and followed their progression for six years. The study revealed that illness perceptions regarding OA symptoms, the level of perceived control over the condition and the perceived consequences of OA were predictive of the level of disability. Those with higher perceived control and less negative emotions had lower disability scores and better functional improvement over the years. The authors also

noted that as some participants improved their understanding of OA, their emotions towards the condition became more optimistic and less negative.

Some studies have indicated that levels of physical activity and adherence with exercise can be improved by discussing positive beliefs, educating people about physical activity and direct recommendation of physical activity and exercise by clinicians (Fransen et al., 2015). The findings of this study show that illness and intervention perceptions can be very important in improving adherence to exercise and optimising its outcomes.

The presence of a social support network can play a significant role in improving engagement and adherence to exercise. This factor was presented by the panel of experts in the Delphi study and achieved >70% consensus. In addition, evidence from a systematic review that included 20 longitudinal studies shows that the presence of a social support network helps in engaging and adherence to exercise (Scarapicchia et al., 2017). However, it was controversial whether the source of support makes a difference in the level of adherence or not. Some studies claim that practical peer support (i.e., doing exercise together) is the best type of support. Additionally, some studies claim that there should be caution about too much support from friends and family as it might make the person feel pressured, leading to a backlash against exercise. (Martire and Franks, 2014).

5.4 Public Patient Involvement

This is the second PPI conducted as part of the IE development process. The first PPI was conducted as part of stakeholders' involvement in chapter 4.

5.4.1 Objectives

- To obtain input from the public and patients on the overall process of developing an optimised IE intervention for people with hip and knee OA.
- To obtain input from the public and patients on the modelling phase of the development of an optimised IE intervention.

5.4.2 Design

The PPI meeting was conducted online using Microsoft Teams video meeting. The meeting was conducted by the primary researcher (K.Y). Lay summary of the context and objectives of the meeting were provided to the PPI members two weeks prior to the meeting. Participation in the meeting was completely optional, and everyone in the meeting was treated with fairness and equality standards.

5.4.3 Participants

The participants were recruited from an existing PPI advisory group in the Pain Centre Versus Arthritis at the University of Nottingham. Invitation letters were sent to 4 potential participants, including details about the time and contribution required for the meeting, and participation was optional.

5.4.4 Ethical consideration

PPI meeting does not require ethical approval. No recording was required. Only notes were taken during the meeting to capture the participants' views anonymously. All data were kept secured by a password on a computer that belongs to the University of Nottingham.

5.4.5 Results

Three participants attended the PPI meeting. The participants (> 50 years old) are diagnosed with osteoarthritis (>3 years ago) and are receiving exercise intervention as part of their treatment plan.

Two of them had read the lay summary prior to the meeting, and the other did not notice the document in the invitation attachment. However, the meeting started with a short presentation that explained the whole research project and the concept of IE.

The main topics were discussed during the meeting are:

- The concept of IE for people OA.

- Personal experience with exercise prescription.
- Process of intervention development.
- The main individualisation factors identified and the process of combining the findings.

A summary of the opinions obtained during the meeting is provided in the table below (Table 5-2).

Table 5-2 Summary of Public Patient Involvement statements

Topic	PPI statements
The concept of individualised exercise	• Individualised exercise should be better and standardised exercise (by definition). • Individualised exercise can be complicated and challenging to implement in clinics. • Individualisation is happening anyway in practice, but it is not very efficient currently. Therapists seem to be trying to personalise exercise without clearly understanding what works better. • Individualised exercise should be an ongoing process because the condition and symptoms change over time.
Intervention development process	• The steps followed in developing the intervention seem to be excellent and holistic. • Identifying the other studies and literature in the field is an important phase. • It would have been great if enough information was found to identify which individualisation method is most effective. • Getting advice and opinion from experts in the field is an important component of the development process.

	• It was suggested that attending and observing live sessions where individualised exercise is being delivered would have generated good inputs to the development process. • More information should be obtained regarding the cost-efficiency of delivering an IE intervention.
The results of the development process	• The list of factors and the modelling process seems to be well inclusive and efficient. • Psychological factors such as self-efficacy and personal goals are extremely important. • The feasibility of including multiple individualisation factors is a bit concerning. However, if done properly, it could lead to much better results. • Even if the individualisation process took a longer duration than standard sessions, it would probably lead to less pressure on the healthcare system in the long term. Patients would probably adhere better to exercise and may not need to return to the service frequently.

5.4.6 Summary of findings

The PPI members provided valuable insight from each of the topics discussed. Overall, they had a good impression of the concept of individualisation of exercise (and all medical treatments). They expressed optimism concerning the potential of IE for OA and how it may boost the effects of exercise and improve the quality of life of people with OA.

In regard to the development process, the meeting attendees initially stated that they had limited knowledge regarding the procedure of intervention development, but at the same time, they felt that the approach followed in this study was sensible and holistic. One of the PPI members suggested adding observation of IE being delivered in practice to analyse and understand the intervention in a realistic manner.

Some PPI members have also expressed concerns about including too many individualisation factors in the treatment sessions. They believe that it may be time-consuming and may not be cost-efficient. However, they also stated that if the time was efficiently controlled to make the intervention more effective and adherable, it is worth trying.

5.5 Logic model: of identifying main components of an optimised individualised exercise intervention

According to the MRC framework, a logic model is an essential component of an intervention development process (Skivington et al., 2021b). Multiple methods can be used to provide a logic model; however, the main components of any logic model should include:

- Inputs/resources.
- Mechanisms to be activated/outputs.
- Outcomes/impact.
- Context of delivery.

The current process of developing an IE programme can be explained in the following logic model.

At first, aim of the intervention being developed should be clarified.
The aims of this optimised IE programme are:

- To improve effectiveness of the intervention by decreasing pain and improving function for people with OA.
- To improve long-term and short-term adherence to therapeutic exercise.

The optimised IE aims to solve two main issues: inconsistent effect of exercise intervention and low adherence rates. Summary of the modelling process can be found in Figure 5-3.

5.5.1 Inputs

The proposed intervention includes the following as the main factors (inputs) of an optimised IE programme:

- Determination of main symptoms
- Assessment of baseline physical activity and muscular performance
- Psychosocial factors: determination of patient's personal goals and discussing social support network.
- Elicitation and discussion of illness perceptions regarding OA and exercise

The purpose of focusing on only four factors is to facilitate a practical, workable application of the proposed IE programme in clinical trials and in practice. Having a high number of IE factors can be confusing and time-consuming for both clinicians and patients. Greater efficiency is likely if more time and focus are given to these four factors of individualisation, which may be able to optimise the benefits of exercise.

The rationale behind selecting these factors was to cover multiple biopsychosocial model aspects related to people with OA. The consideration of this model is illustrated in the following. First, disease-related factors linked to the complaint's main symptoms were taken into consideration. Second, the person's physical condition was considered by assessing baseline physical capabilities. Third, the psychological and social aspects were considered by discussing personal goals and setting targets from personal perspectives as a source of motivation. Moreover, discussing the possibility of having a social support network as it may help to engage the person in exercise and make it more sustainable. Details and justification of each individualisation factor will be illustrated in section 5.6.

5.5.2 Outputs

The proposed IE intervention that focuses on the IE factors illustrated earlier (the input) is expected to lead to the following outputs:

1- Improvement in the physical condition of the person complaining of OA based on the individual’s needs. Improvement in the physical condition will be based on the individual’s needs (e.g., strength, endurance and flexibility), which are identified by assessment of baseline physical activity and muscular performance. This is

expected to be more effective in decreasing pain and improving function than a generalised exercise prescription.

2- Improvement in self-efficacy levels by considering personalised goal-setting and motivation as behavioural change techniques. Improving self-efficacy regarding arthritis, exercise and self-management is among the key outputs targeted in this intervention.
3- Gain positive beliefs about OA and exercise in addition to positive outcome expectations. It is expected that this outcome will be achieved by understanding the illness perception of the person and providing individualised education about OA and exercise.

5.5.3 Outcomes to be achieved

The flow of the logic model infers that appropriately considering the IE factors (inputs) in exercise prescription for hip and knee OA patients is predicted to lead to the three main outputs desired (physical condition, behavioural changes, and positive beliefs). These outputs should eventually provide a positive effect on the primary outcomes of the intervention.

The primary outcomes targeted by this intervention are:

1- Pain reduction.
2- Improvement in function.
3- Long-term adherence to exercise.

5.5.4 Context of delivery

The logic model's components (input, output, and outcome) can all be affected by the context of delivery. Different components of the intervention can interact with the context in a way that can positively or negatively affect the outcomes. Therefore, the following is a proposed optimal context for IE delivery in which some extent of flexibility is allowed.

In an optimal context, IE is prescribed for people with hip or knee OA in a physiotherapy clinic. The treatment session is delivered by a qualified physiotherapist. The IE intervention involves multiple types of exercises, including strengthening, aerobic or flexibility. The intervention is delivered in a standard physiotherapy clinic or gym. All safety measures and basic equipment are provided.

The choice of location is flexible and depends on personal preference. However, there are some advantages and disadvantages to each context. For example, undertaking exercise at home can be convenient for most people, but sometimes people tend to be too relaxed at home and do not pay the necessary attention to quality and performance. In contrast, doing exercise in groups may be a source of motivation. The cultural and social barriers to exercise should be discussed and taken into consideration. Exercise can also be linked to daily activities (e.g., before having a

morning shower), so it becomes a daily routine and part of lifestyle rather than a “treatment” that needs to be specially catered for.

Number and duration of treatment sessions are similar to standard physiotherapy sessions for people with OA. Therefore, there will not be any additional cost on the health care systems. Assessment of individualisation factors is also within the scope of practice of qualified physiotherapists. Therefore, no additional training is required. In contrast, if the intervention achieved better adherence this will lead to making the patient less dependent of health care system there less load on physiotherapy services.

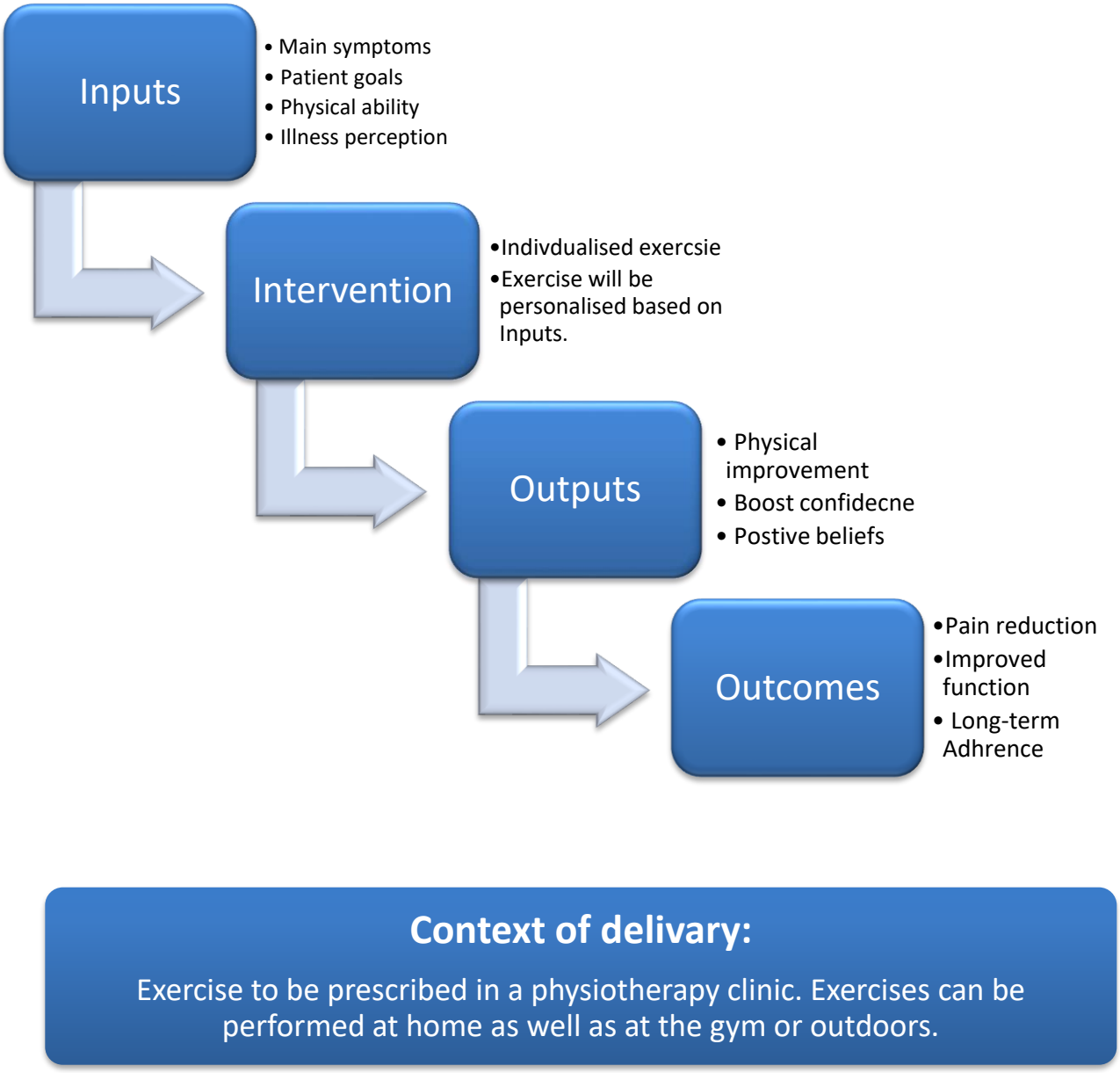


Figure 5-3 Summary of modelling process

5.6 Individualisation factors

Numerous individualisation factors were identified in this study. Some were identified in the systematic review and others from the Delphi study. However, prioritising and identifying the most relevant factor that should be included in an optimised IE intervention is challenging. Designing such an intervention should consider including the most important factors and factors that complement each other to ensure the individualisation process is holistic and covers important aspects (e.g., physical, and psychological)

The following four IE factors were eventually identified for this intervention:

- Determination of main symptoms
- Assessment of baseline physical activity and muscular performance
- Psychosocial factors: determination of patient' personal goals and discussing social support network.
- Elicitation and discussion of illness perceptions regarding OA and exercise

A rationale for each of the components is illustrated in Table 5-3 and Figure 5-4.

Table 5-3. Main components of an optimised IE intervention

IE factor	Evidence	Theory
Main symptomatic complaint	• Identified in systematic review results • Achieved high consensus in Delphi vote.	• Specific type of exercise can work better to improve specific outcomes
Psychosocial factors	• Achieved high consensus in Delphi vote. • Supported by literature and theories. • Important components of biopsychosocial model.	• Setting goals is a source of motivation. • Achieving small goals improves self-efficacy. • Presence of social support network may enhance engagement in and adherence to exercise.
Assessing baseline strength and physical activity	• Identified in systematic review results • Achieved high consensus in Delphi vote. • Supported by exercise prescription guidelines.	• Assessing baselines abilities helps identifying patient needs. • Understanding current patient abilities ensures starting of exercise programme at right level of intensity. • Starting from low difficulty and gradually progressing leads to better adherence.
Illness perceptions	• Achieved high consensus in Delphi vote. • Supported by literature and theories.	• Misperceptions about osteoarthritis and exercise are barriers to adherence. • Having appropriate perceptions about benefits of exercise improves confidence and motivation to exercise.

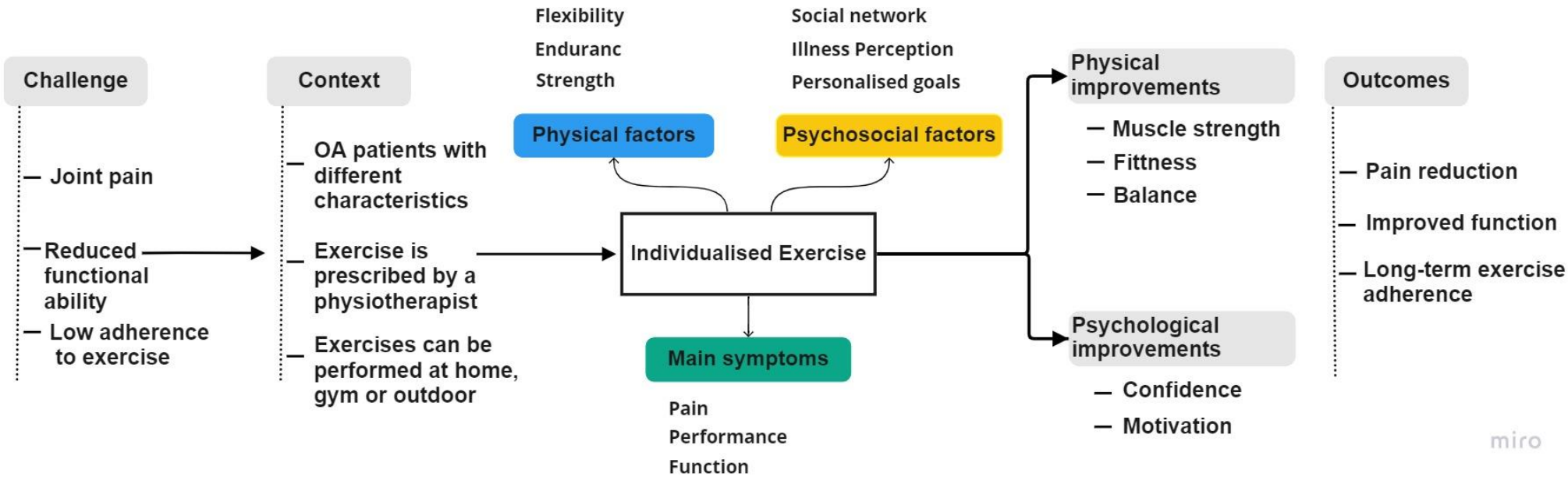


Figure 5-4 Modelling of an optimised individualised exercise intervention for people with hip and knee osteoarthritis

5.6.1 Main symptoms

To prescribe an IE intervention for people with OA, assessing the types and severity of symptoms is important to obtain the best possible outcomes (NICE, 2014). Main symptoms such as pain and functional limitations should be assessed, and exercise characteristics should be tailored to match the person's needs and tolerance. For example, for a person complaining of severe pain, the exercise prescribed should consider what the person can tolerate and should progress with caution so as not to aggravate the pain any further. Thus, alternative exercise options such as isometric, water-based and non-weight bearing can be prescribed.

In the SR, individualising of exercise according to OA symptoms was used in 3 RCTs out of the 10 that provided IE for people with OA (Allen et al., 2018a, Foroughi et al., 2011, Skou et al., 2015). Severity of symptoms (mainly pain) and performance are the most frequently used IE factors in OA.

In the study by Allen et al. (2018a), exercise difficulty was tailored according to pain severity and functional ability where participants were assigned to one of 7 exercise difficulty levels. This study provided evidence that this intervention had positive effects on pain and function outcomes. The other two studies that have IE based on severity of OA symptoms, focused on maintaining the exercise intensity within bearable

limits of pain whilst maintaining the quality of exercise performance (Foroughi et al., 2011a, Skou et al., 2015).

The expert panel in the Delphi study also emphasised the importance of OA symptoms as a factor for IE prescription. The panel of experts concurred on a 95% agreement level to consider pain severity as an important IE factor for OA. The stakeholders also agreed that considering OA symptoms when individualising exercise is very important.

Furthermore, recent literature suggests that different types of exercise should be used according to the main symptom, and modification of the intensity of exercise is recommended in cases of symptom exacerbation. A NMA has been used to test the effect of different types of exercise on specific outcomes of OA (Goh, 2018). This study has revealed that aerobic exercise alone can be more effective for pain management than strengthening exercises alone and mixed types of exercise. Additionally, the study has shown that strengthening exercises are more effective in improving functional outcomes when compared to aerobic or mixed exercises.

Furthermore, symptomatic flare-ups are linked to low adherence to exercise in OA patients (Marks, 2012, Roddy et al., 2005b). A recent study by Henriksen (2014a) has developed a standardised exercise

programme for people with knee OA that involves specific modification for days of flare-up of symptoms. This exercise programme for people with a current high level of pain is known as a rescue session. In this session, the exercise programme is modified to avoid weight-bearing exercises as well as any other activity that aggravates pain (Bartholdy et al., 2017). Overall, the study suggests that the adherence level of people with high levels of pain is improved with rescue sessions rather than with the same form of exercise being continually repeated without breaks, regardless of symptom fluctuations. (Bartholdy et al., 2017).

5.6.2 Psychosocial factors

The expert panel in the Delphi study also emphasised the importance of patient goals and social support network as factors for IE prescription. Patient goals were one of two items to achieve 100% agreement level and be considered for inclusion as an important IE factor for OA. The stakeholders also suggested designing the treatment plan based on SMART (Specific, Measurable, Attainable, Relevant and Timely) goals decided by patients and therapists. Goal setting is an important psychological factor that provides sustainable motivation to exercise. Additionally, presence of social support network (if available) can be a good source support towards engaging into exercise and adherence. This

social factor was accepted by the Delphi panel (72%) and is one of the three pillars of the biopsychosocial theory for interventions.
Evidence from the literature on the importance of goal setting and the importance of a social support network was presented earlier in section 5.3.2.

5.6.3 Baseline physical activity and muscular performance

Justification for prioritising these factors over others available come from the results of the SR and the Delphi study. Baseline physical activity and muscle performance can be categorised under the term “physical capability”, which gained 100% agreement in the Delphi study. In addition, baseline physical activity and baseline muscle strength were also separately mentioned as IE factors by the Delphi panel with both achieving a 91% consensus.

In the SR, three studies based their IE on baseline performance of participants. Testing performance provides an alternative method for testing physical ability of the person. Whether the testing involves strength or endurance, it can be categorised under assessment of baseline capabilities. However, there was a lack of detail on how physical assessments were carried out and how exercise was prescribed for different physical abilities.

Additionally, guidelines for exercise prescription published recently by Bangor University (ESRC, 2021) have stated that testing baseline abilities of patients is important has it achieves three key objectives:

1. Prescribing realistic exercise targets.
2. Good evaluation of progress by comparing results of follow-up assessments.
3. Source of motivation, as the patient sees improvement with every session and compares it to their baseline.

Maintaining a good level of physical activity is known to have many health benefits, such as improving cardiovascular health, respiratory health and psychological well-being (WHO, 2011a). However, it should be noted that a direct relationship between increasing physical activity and pain reduction in joints has not yet been established. A recent longitudinal data analysis of a three-armed exercise intervention - in the form of an RCT- on people with chronic knee pain highlighted no association between change in physical activity and clinical outcomes such as pain and function (Quicke et al., 2018). However, the authors of the study implied that people with knee pain should still be advised to maintain a good level of physical activity to attain the general health benefits associated with physical activity.

5.6.4 Illness perception regarding osteoarthritis and exercise

In this component, the focus is on assessing and improving the person's perception regarding OA and the role of exercise in OA management. Education is a part of exercise prescription. The therapist educates the patient about how to perform specific exercises to improve their medical condition. Therapists should also explain the purpose of doing these exercises and how they improve the person's condition and overall health. Making sure the person has appropriate perceptions and beliefs about exercise is an essential factor in attaining engagement with the therapists and to ensure adherence for longer periods. Therefore, this component is considered essential to the success of an optimised IE intervention.

None of the existing IE studies for OA have considered using illness perception, or any form of constructed education about OA and exercise, as an individualisation factor. However, in the Delphi study, 78% of the panel of experts voted to include illness perception as an IE factor. Illness perception was also discussed during the stakeholders' meetings and received considerable attention, especially by patients attending the first meeting. These patients stressed the importance of therapists listening to their beliefs about OA and exercise to provide a successful IE intervention. This would enable any misconceptions about OA and/or exercise to be corrected.

5.7 Summary of the development process

The development of an optimised IE is a long undergoing process. This research project follows the recent MRC framework for developing complex interventions. This framework infers that the development process is a continuous development cycle, feasibility testing, evaluation, and implementation.

The progress made so far in developing an optimised IE intervention falls in the initial development stage. A significant amount of information was collected from the SR and analyses, the Delphi study, and stakeholders' involvement. This was followed by the synthesis stage, where this information was described within the MRC framework providing relevant underpinning theory and logic model. As a result, four individualisation factors were introduced to form the IE intervention. This optimised IE intervention will then be tested in the acceptability study proposed in Chapter 6.

Although this study has succeeded in producing important information concerning IE for people with OA, there are multiple limitations to the development process. Involving stakeholders in the study was limited. Stakeholders could have been involved early on in identifying and prioritising research questions, co-development of programme theory and

other parts. However, further stakeholders' involvement can still be done in the future stages of the development process, such as overcoming practical obstacles to evaluation and implementation, re-evaluation of the intervention and planning subsequent development stages as suggested in the recent update of the MRC framework (Skivington et al., 2021b).

Additionally, alternative methods could have been used in consulting experts and other stakeholders'' to prioritise the IE factors. Another limitation of the study is that it focused mainly on collecting quantitative data about IE and limited qualitative input. Given the nature of IE, having multiple physical and psychosocial components, it would have been insightful to gather qualitative data to understand the intervention comprehensively. For example, this could be done by interviewing patients and therapists, seeking their personal experiences and opinions in this regard. An economic evaluation of the proposed intervention is also limited. There is a need to understand how feasible it is the delivering an optimised IE, and this needs to be tested in the future stages.

Chapter 6. A protocol for an acceptability study of an individualised exercise programme for people with osteoarthritis

6.1.1 Aim

The purpose of this study is to test the acceptability of an IE intervention for people with knee OA.

The study will exclusively examine people with knee OA (not hip and knee) due to recruitment limitations. The recruitment process relied on the KPIC database which includes only people with knee pain.

6.1.2 Objectives

- To test the acceptability of an IE intervention by assessing patient satisfaction.
- To assess the change from baselines in pain and physical function outcomes during the intervention.
- To test the feasibility of conducting the trial by assessing the process, which includes testing the feasibility of the eligibility criteria and a resources assessment (e.g., time, space and equipment).

6.2 Methods

6.2.1 Study design

This study will be a one-armed pre-test/post-test intervention study. There will not be a control group.

6.2.2 Overview

The primary outcome for consideration will be patient satisfaction. Secondary assessments include: process assessment, resources assessment, adherence, pain, function, physical activity, muscle strength and illness perception. Assessments of pain, physical activity, muscle strength and illness perception will be used to individualise the exercise intervention for this study.

The intervention will mainly involve prescribing therapeutic exercises. These will be taught during the visits and patients will be instructed to subsequently perform these exercises regularly at home. Assessments will be made at every visit.

6.2.3 Duration of the study

The study is expected to take up to six months. Each participant will be involved in the intervention for 3 months. During this period, the participant

is required to attend the clinic 8-12 times, each visit being approximately 45 minutes.

6.2.4 Recruitment of participants

The study will recruit 20 participants with chronic knee pain. Participants will be recruited through registries of people with knee OA held by the University of Nottingham from previous studies including KPIC (Fernandes et al., 2017b) and the Biomedical Research Council (BRC) survey.

The study team in the Academic Rheumatology department will invite potential participants via mail (Appendix 11: Invitation letter). The invitation will include a patient information sheet and reply slip (Appendix 12: Invitation Reply Slip Appendix 13: Patient information sheet). Participants can respond via a reply letter, a telephone call or an email.

Potential participants will be screened for eligibility by phone and can further discuss all aspects of participation in the study. It will be explained to the potential participants that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. Moreover, they will be informed of their ability to withdraw at any time, although attempts will be made to avoid such occurrences wherever possible. In the event of their withdrawal, participants will be informed that

their data collected so far cannot be erased and consent will be sought to use the data in the final analyses where appropriate.

Participants who are eligible and wish to participate in the study will be invited to attend an initial baseline assessment. All participants will provide written informed consent prior to any assessments (Appendix 14: Consent form).

6.2.5 Participants

Participants who meet the following inclusion criteria will be eligible to participate in the study:

- Unilateral or bilateral moderate-severe knee pain for most days of the previous month and knee pain for at least 3 months in the past year.
- Age: adult aged over 40 years.
- Able to read and write in English.

The following exclusion criteria will be applied:

- Inability to give informed consent.
- Terminal or severe mental illness.
- Unstable heart condition.

- Neurological conditions (stroke, multiple sclerosis, Parkinson's disease, motor neuron disease, muscular dystrophy, Huntington's disease), inflammatory joint diseases including rheumatoid arthritis, gout or calcium pyrophosphate crystal arthritis, and dementia.
- Acute soft tissue injury to the knee within the last 3 months.
- On waiting list for total knee replacement surgery.
- Intra-articular corticosteroid injection in the knee in the previous 6 months.

6.2.6 Study intervention

An IE intervention for participants, including an education component (detailed below) will be delivered by a single therapist. Two types of exercise will be prescribed as part of the individualisation process: local muscle strengthening and aerobic exercise. Each individual's needs will be assessed, and the appropriate type of exercise assigned accordingly. The participant progress from the initial invitation right up until final visit is shown in Figure 6-1.

The prescribed programme will have a standard version for aerobic and local strengthening exercises. However, the exercise programme will be modified for each participant according to the following individualisation factors:

- Determination of main symptom
- Patient’s goals
- Assessment of baseline physical activity and muscular performance
- Elicitation and discussion of illness perceptions regarding OA and exercise

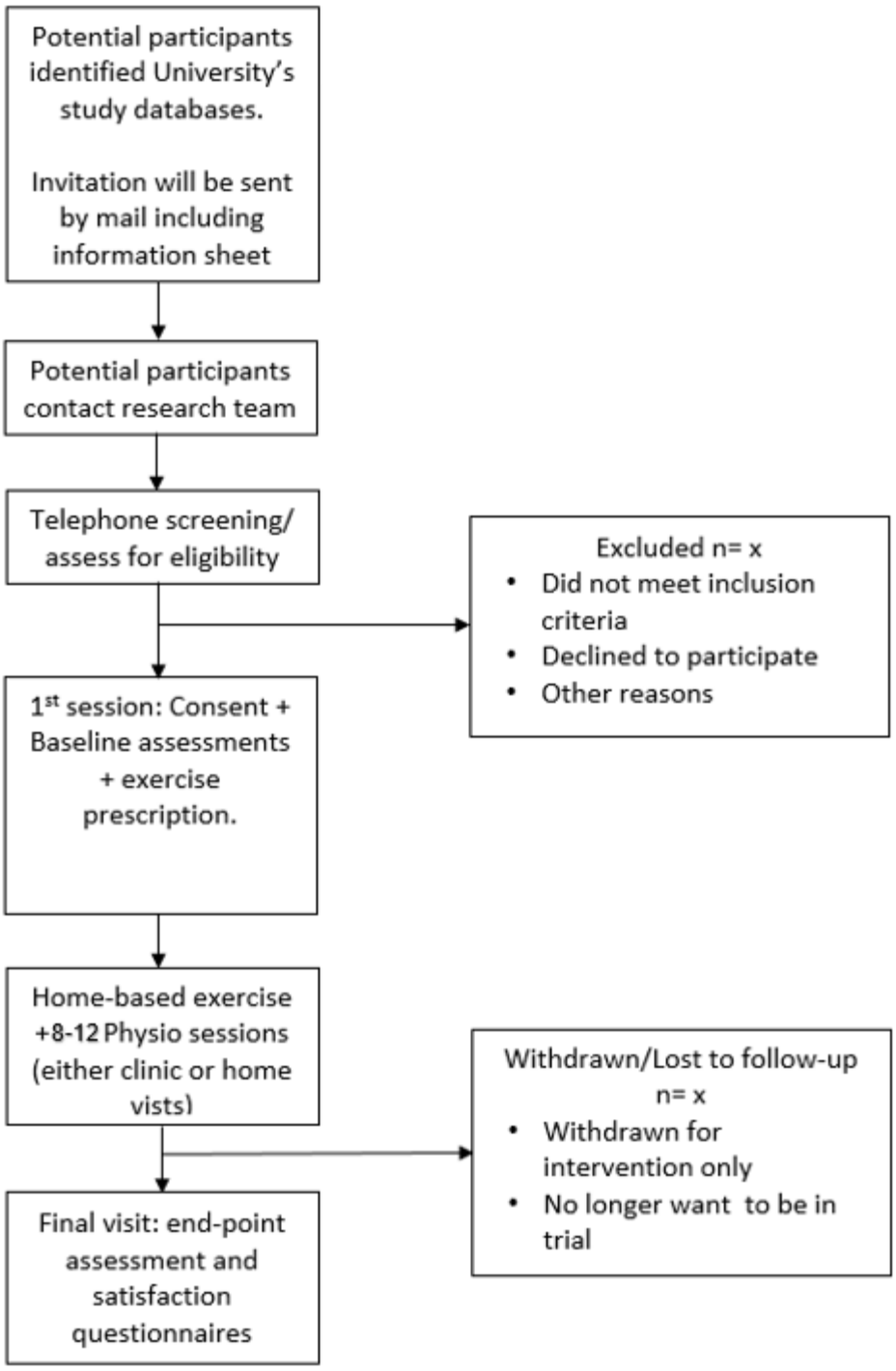


Figure 6-1. Participant progress through the study

Session details

Participants will be invited to attend the Academic Rheumatology Department in the Clinical Sciences Building at Nottingham City Hospital. As the intervention in this study is an IE, the first session will involve assessment for individualisation factors. Firstly, the person will be asked about what they aim to achieve in physiotherapy sessions and their main symptomatic complaints in relation to their OA knee(s). Severity of symptoms will be assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS) for pain and function (Roos and Lohmander, 2003). This will help identify the main goal for the person, (e.g. returning back to specific activities or pain reduction) which will be discussed with the person to set short-term and long-term goals. The main aim of setting these goals is to motivate the participants to adhere to the exercises. These goals can be updated and modified regularly. Each goal should be measurable, attainable and time-bound.

Secondly, baseline physical activity level and muscle strength will be assessed. Physical activity will be assessed using the International Physical Activity Questionnaire – Short Form (IPAQ-SF) (IPAQ-SF, 2002). This will be compared to the international standards for physical activity as defined by the World Health Organisation (WHO, 2011a, WHO, 2011b). All participants will be encouraged to maintain a healthy level of physical activity. Thirdly, the patient's level of illness perception will be assessed

using the Revised Illness Perception Questionnaire (IPQ-R) (Moss-Morris et al., 2002).

The intervention will start from the first visit and continue for 12 weeks. During this period, the patient is expected to have 8-12 sessions where exercise will be revised and modified if needed. These sessions can be delivered during visits to the rheumatology department or home visits, depending on each participant's preference. The final visit will include end-point assessment for all outcomes, including a satisfaction questionnaire.

Table 6-1. Summary of individualisation process

Individualisation steps	Intervention
Step 1: Assessment of illness perception	• Individualised education about OA and exercise
Step 2: Identifying patient's goals and presence of social support network.	• Patient will be asked about their own goals. • Short-term and long-term goals will be decided with patient. • Goals can be specific activities to be performed, restoration of specific function, and/or specific degree of pain reduction. • Goals can be revised and updated regularly. • Discussion about the possibility of having support from family and friends to exercise. The support can be by verbal encouragement or exercising together, No specific assessment is needed to determine this factor.
Step 3: Identifying main symptomatic complaint	• If pain is the main complaint: emphasis will be on aerobic exercise. • If functional disability is the main complaint: emphasis will be on strengthening exercises. • Physical activity will be encouraged for all patients.

Step 4: Assessment of baseline muscle strength and physical ability	• For aerobic exercise: minimum aerobic ability will be identified first (by calculating maximum heart rate). An individualised aerobic programme will be designed to improve aerobic fitness. • For strengthening exercises: assessment of current muscle strength will be done first (using 1 RM method). An individualised muscle strengthening programme will be designed to improve muscle strength.

1 RM = one-repetition maximum

6.2.6.1 *Intervention details*

The intervention involves two individualised components: education and exercise. The section below provides a summary of the individualisation process as outlined in Table 6-1.

6.2.6.1.1 Education

Specific individualised education about OA and exercise will be provided to the participants. The information provided will be based on recent updates from international guidelines (NICE, 2014, Fernandes et al., 2013, Bannuru et al., 2019). Results of the IPQ-R will help identify any misconceptions that need specific clarification.

This educational component will involve three stages. First, the current level of illness and intervention perception will be assessed. Misconceptions and excessive worries will be noted. Second, the therapist will explain to the participant the nature of OA, expected prognosis and role of exercise and physical activity. Specific focus will be placed on the areas of misconceptions, motivation, and reassurance. Third, the participant will be given three educational booklets published by Versus Arthritis (formally known as Arthritis Research UK). The first is a booklet explaining what knee OA is and how can it affect a person's life (ARUK, 2013b). The second booklet is related to pain education for patients with OA and is titled "Pain and Arthritis" (ARUK, 2013a). The third booklet is related more to coping with OA in the activities of daily living, and is titled "Everyday Living and Arthritis" (ARUK, 2013a).

The educational component will also involve providing simple advice about the general benefits of exercise, and specifically its benefits for OA management. The information provided will be based on NICE recommendations.

6.2.6.1.2 Exercise

Exercise prescription in this study will be in line with exercise prescription guidelines from the ACSM (Liguori, 2020). Participants will receive advice to perform both strengthening and aerobic exercises as recommended by

NICE guidelines (NICE, 2014). However, for individualisation purposes there may be more emphasis on one type of exercise according to the participant's main complaint. Although both strengthening and aerobic exercises need to be done optimally, recent evidence has shown that focusing on one type at a time can lead to better outcomes (Goh, 2018). Thus, if pain is the main problem, the patient will receive mainly aerobic exercises. However, if functional ability is the main problem for the patient, then the intervention will involve a higher proportion of strengthening exercises. Additionally, severity of symptoms will also be considered. The person can exercise if the exercise does not provoke more pain or if the pain is tolerable. However, in case of severe pain with exercise, the patient will be instructed to do light isometric or isotonic exercises and to progress gradually.

For specific functional limitations, the person can do task specific exercises. If the person aims to be able perform a specific task (e.g. use the toilet or walk a specific distance), an individualised task specific exercise program can be provided. For example, doing that task gradually and daily until it can be done optimally with minimal pain, or doing specific exercises that help in improving the performance of that task.

A- Strengthening

The muscle strength test will guide the individualising of the intensity and rate of progression of the strengthening exercise. The level of resistance (load) of the strengthening exercise will be determined according to the results of an individualised muscle test. The muscle testing method to be used is the one-repetition maximum (1 RM) method (Kraemer et al., 1995). First, in order to calculate the 1 RM, the person is asked to perform 4-6 repetitions of exercise against the maximum possible resistance weight. Once that has been completed, the following equation will be used to calculate the 1RM of that person: (The weight used in the 4-6 repetitions X 1.1307) + 0.6998 = 1RM.

Once the 1 RM has been obtained, resistance used in exercise sessions will be around 60% of the maximum ability of the person. The ACSM standardised exercise plan for resistance training will be followed and is detailed below:

- Resistance can be free weight, Thera-band (resistance elastic band) and/or exercise machines.
- Number of sets should be 2 or 3 sets, with 8-12 repetitions in each set.
- Movement to lift and lower the weight should be performed in a controlled manner.

- The final repetition of each set should be difficult. The level of weight resistance should increase with each set to make it challenging.
- All exercises should be performed at least 2-3 times per week.

The strengthening exercises that will be delivered in this study are:

- Isometric quadriceps exercise.
- Straight Leg Raise (SLR).
- Sitting Knee extension.
- Resisted knee extension/flexion.
- Hip flexion/extension/abduction exercise.
- Supported squat (Back on wall).

B- Aerobic

Five main types of aerobic exercise will be prescribed in this study:

- Walking.
- Cycling.
- Swimming.
- Functional aerobic exercise with different difficulty levels (example in Appendix 15: Functional exercise).
- Chair based aerobic exercise (example in Appendix 16).

One or more of these types can be chosen according to personal preferences/ abilities. The intensity and duration of the exercise session will be determined according to the baseline abilities of the patient. The exercise should increase the heartrate and achieve slight breathlessness for the participant. Calculating an individual's aerobic capacity is related to maximum heart rate (McArdle et al., 1991).

- Moderate-intensity aerobic exercise = increase of heart rate to about 50%-70% of maximum heart rate.
- Vigorous-intensity aerobic exercise = increase of heart rate to about 70%-85% of maximum heart rate.

The target level for average dose of aerobic exercise to reach the minimum physical activity level as recommended by WHO is as follows:

- Adults aged 18 and older should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous- intensity activity (WHO, 2011a).

6.2.7 Outcomes

6.2.7.1 *Primary:*

1- Satisfaction: the Physiotherapy Outpatient Satisfaction Questionnaire (PTOPS) (Hills and Kitchen, 2007) will assess participants' satisfaction with the intervention. PTOPS is a recognised patient satisfaction tool that has previously been used to assess patients' satisfaction with exercise intervention in OA management (French et al., 2010). The questionnaire is shown in Appendix 16.

6.2.7.2 *Secondary:*

1- Process assessment: this assessment will focus on the feasibility of the eligibility criteria, recruitment rates and follow-up rates.
2- Resources assessment: this assessment will answer questions about time, equipment, space and other resources needed to conduct the study. This information will be recorded to enable estimation of requirements in future trials.
3- Adherence: the participant's attendance rate and home-exercise record will be collected at each visit. The home-exercise programme will be recorded in an exercise recording logbook.
4- Pain and function: the Knee Injury and Osteoarthritis Outcome Score (KOOS) for pain and KOOS for function will be used (Roos and Lohmander, 2003).

5- 30-second sit to stand test (Rikli and Jones, 1999).
6- Physical activity: the International Physical Activity Questionnaire - Short Form (IPAQ-SF) (IPAQ-SF, 2002) (Appendix 18).
7- Muscle strength: hand-held dynamometer muscle testing will be used (Wang et al., 2002). The strength will be calculated from the mean results of three contractions. Muscle testing will assess strength of knee extensors and flexors.
8- IPQ-R (Moss-Morris et al., 2002) will be used (see IPQ-R assessment form attached in Appendix 19.

It should be noted that all self-reported questionnaires are subjected to recall bias.

6.2.8 Analysis

The researcher conducting the research project (KY) will oversee the statistical analyses under the guidance of Prof Weiya Zhang (Professor of Epidemiology). The data will be entered into Microsoft Excel and Statistical Package for the Social Sciences (SPSS). Each participant will have an individual record for his/her baseline and progress assessments. Recruitment, enrolment, and retention rates in relation to the study and the intervention will be calculated by descriptive statistics reporting frequencies and percentages. Baseline characteristics will be summarised for the study group. Descriptive statistics will be used to present the

results of the satisfaction questionnaire (measured only once at the end of the trial). Change in clinical outcomes (pain, physical function, physical activity, muscle strength) data will be analysed using the paired T-test or the Wilcoxon signed-rank test, if the data are not normally distributed.

The results of the study will be available to the study management group. All data will be stored and secured in Academic Rheumatology department and will be backed up on the University of Nottingham servers. ES will be examined by calculating the standardised mean difference (SMD) between the post-intervention mean and the pre-intervention mean, divided by the pooled standard deviation.

6.2.9 Study management

The study will be managed in the Academic Rheumatology and Clinical Sciences Building by the Research Manager under the supervision of the Chief Investigator, Dr Michelle Hall, who has overall responsibility for the study and shall oversee all study management.

Other members of the team are Prof Weiya Zhang (Professor of Epidemiology), Prof Michael Doherty (Emeritus Professor, University of Nottingham) and Prof Abhishek (Professor of Rheumatology, Faculty of Medicine & Health Sciences).

The study management group will meet regularly and have documented monthly meetings from the outset of the study. The group will also monitor and supervise study progress as well as discussing and advising on recruitment rate and unforeseen logistical issues to ensure that its objectives are achieved.

6.2.10 Commentary on study progress

6.2.10.1 *Ethics*

The Research Ethics Committee (REC) granted approval for this study on 11 February 2020 (Appendix 20). Relevant Good Clinical Practice (GCP) training was completed on 10 March 2020 (Appendix 21).

6.2.10.2 *Recruitment*

Invitations were sent to 53 potential participants; 12 were recruited, 5 rejected the invitation and the remainder did not respond. The participants were invited to start attending the sessions by the end of March 2020. However, all invitees were contacted and informed that the study would no longer be taking place due to the COVID-19 pandemic.

Chapter 7. Discussion

In this thesis, an SR with CMA and NMA and a Delphi study with stakeholders' meetings were conducted to develop an optimised IE intervention for hip and knee OA. The intervention was structured and a protocol to test its acceptability was developed. This intervention development process is in keeping with the MRC framework for developing complex interventions.

7.1 Thesis novelty

1. The first SR to attempt to identify the IE studies in the management of OA.
2. The first CMA analysis to compare the effects of IE versus usual care and the first NMA to compare IE versus NIE.
3. The first study to develop consensus on the optimal strategies to individualise exercise for people with OA.
4. The first proposed IE exercise that has multiple individualisation factors identified based on a verified intervention development framework (MRC).

7.2 Summary of findings

In the SR, a CMA of RCTs was conducted comparing efficacy of IE versus usual care and efficacy of NMA versus usual care. In both comparisons, exercise (IE and NIE) was found to be better than usual care; however, IE had higher ES than NIE. To obtain a more precise estimation of IE effects, indirect evidence was used through NMA to compare the ES of IE versus NIE. ES of IE was consistently higher than NIE in all outcomes; however, 95% of CI overlapped for performance and QoL outcomes, which made it a non-significant difference. Probability ranking, however, demonstrated that IE was the best option for treatment based on SUCRA scores. Additionally, the review identified the most common ways used to provide IE for people with OA. Individualisation of exercise based on performance-based progress and individualisation based on severity of symptoms were the most common methods. Other methods of exercise individualisation were also used, including presence of comorbidity, gait analysis, the most affected compartment of the joint and assessment findings.

Subsequently, a Delphi study was conducted to form expert consensus (as a group) on the optimal strategies to individualise exercise for people with OA. A list of 28 exercise individualisation factors were identified. The top factors were individualising exercise based on patient goals and individualising exercise based on baseline physical capability (both achieved 100% consensus). A further five individualisation factors scored

a 95% agreement level. These were patient preferences, balance, frailty, pain aggravating factors and pain severity.

The Delphi study was followed by a stakeholder engagement meeting. The stakeholders' panel comprised healthcare professionals and people with OA. The purpose of the meeting was to discuss optimal strategies to provide IE intervention from different perspectives. The stakeholders supported the results of the Delphi consensus and emphasised the importance of specific factors such as illness perception and psychosocial well-being.

The results of these studies, as well as evidence from wider literature, were used to inform the development of IE intervention. Four main individualisation factors were identified and considered as the most important factors to provide IE intervention for people with OA. These factors were:

- Determination of main symptoms
- Assessment of baseline physical activity and muscular performance
- Psychosocial factors: determination of patient' personal goals and discussing social support network.
- Elicitation and discussion of illness perceptions regarding OA and exercise

Subsequently, a protocol for an acceptability study was developed to test the acceptability of the developed intervention. Although the acceptability study was not conducted because of the COVID-19 pandemic restrictions, designing the intervention for the study provided some useful insights. It demonstrated that combining multiple individualisation factors in one study is a challenging process. Testing the effects of each IE factor requires specified assessment methods and practical structure for utilization in the intervention provided during the study. All these need to be planned and recorded. Thus, testing an IE programme may require a considerable amount of time and effort from a collaborating research team. Additionally, A future acceptability study may show how much this prolonged process is acceptable and tolerable for participants. This is particularly important, as the level of acceptability of interventions is correlated with adherence (Hommel et al., 2013).

7.3 Findings in relation to previous literature

A considerable amount of literature has concluded that exercise is one of the most important interventions for people with OA. However, the need to optimise the results of and adherence to exercise has also been discussed. IE was recommended by EULAR guidance as a promising method to improve exercise prescription for people with OA.

The current study has investigated the effects of IE, identified a variety of individualisation methods and developed a protocol to test a potentially optimised version of an IE for people with OA.

7.4 Limitations

This thesis is the result of research work conducted over three years that had to deal with a unique and unprecedented pandemic situation which directly affected the progress of the study. The lockdown measures led to an immediate cessation of the acceptability study. This caused a limitation in the results of the overall study project, even though this was compensated by presenting the protocol of the study and the addition of network meta-analysis.

Additionally, it must be acknowledged that developing an optimised package of a complex intervention such as exercise is challenging. Exercise is an intervention that has multiple interacting factors that can affect its results. These factors include some that are exercise specific (e.g. type, intensity and duration) and others that are related to the person receiving the intervention (e.g. physical condition, perceptions and goals).

The study identified an extensive list of factors (28 factors) that holistically cover most of the potential factors that can affect the results of exercise

prescription. However, only four factors in total were prioritised to be tested in the acceptability study due to specific reasons illustrated earlier (time, resources and practical reasons).

7.5 Considerations for future research

As guidance from the MRC framework emphasises (Craig et al., 2013), the evidence developed during a study should progress to develop relevant theories to identify underpinning mechanisms that make this intervention work. Understanding the underpinning mechanisms of an intervention is an essential component of developing a complex intervention. Additionally, a modelling phase is important to refine the developed intervention. The development process should also benefit from testing of the acceptability and feasibility of the intervention to improve the intervention study process prior to testing in a full-scale RCT.

The SR highlights the need for additional clinical trials and RCTs of IE for hip and knee OA, as the number of studies identified was relatively small. Furthermore, future studies should seek to be more comprehensive in terms of testing the remaining factors in further trials as they may identify additional key factors that lead to the optimisation of IE. In addition, the effect of IE on adherence to exercise also requires further investigation. There is a need to understand whether people with OA adhere better to IE

than expected or not. It is also important to understand which individualisation factors help improve people's adherence and how to optimise them.

Further research is required to establish a clear basis for exercise individualisation with regard to both patient and exercise characteristics. This is particularly important to guide clinicians in practice in following a solid evidence-based criterion for individualising intervention.

7.6 Conclusion

Based on the data gathered during this study, it has been demonstrated that IE is beneficial for people with hip and knee OA. IE is significantly better than usual care and is potentially superior to NIE. Individualising exercise is a complex procedure and has multiple interacting components that affect its outcomes such as patients' and exercise characteristics. IE is poorly described in current RCTs and needs further trials to understand optimal ways of providing IE intervention. According to the consensus of a panel of experts, there are up to 28 important individualisation factors that could be considered when prescribing and individualising exercise. These factors involve biological, psychological, and social aspects that affect the choice of exercise and methods of delivery to be provided to people with OA. Developing a complex intervention is an ongoing process, and the results detailed in this study constitute a part of this process. It is clear that further research and trials must be conducted to continue the exploration, development and optimisation of IE intervention for people with hip and knee OA.

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Appendices

Appendix 1: Search strategy

MEDLINE Search strategy for IE for OA management:

Logged in as Khalid Yaseen at University of Nottingham

Ovid MEDLINE(R) <1946 to February Week 4 2018>

1 exercise/ or physical conditioning, human/ 89976 Advanced
2 Circuit-Based Exercise/ 27 Advanced
3 exercise therapy/ or motion therapy, continuous passive/ or muscle stretching exercises/ or plyometric exercise/ or resistance
training/ or hydrotherapy/ or rehabilitation/ or "activities of daily living"/ or dance therapy/
116717 Advanced
4 muscle strength/ or physical endurance/ or anaerobic threshold/ or exercise tolerance/ or physical fitness/ or postural balance/
or posture/ or psychomotor performance/ or "range of motion, articular"/
230898 Advanced
5 Pliability/ 4195 Advanced
6 movement/ or motor activity/ or exercise/ 241218 Advanced
7 Physical Exertion/ 55128 Advanced
8 Mind-Body Therapies/ 840 Advanced
9 running/ or jogging/ or swimming/ or walking/ 59351 Advanced
10 Isometric Contraction/ 14237 Advanced
11 exercise movement techniques/ or breathing exercises/ or qigong/ or tai ji/ or yoga/ or pilates.mp. [mp=title, abstract, original
title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare
disease supplementary concept word, unique identifier, synonyms]
6590 Advanced
12 propriocepti$.ab,ti. 8328 Advanced
13 balanc$.ab,ti. 215086 Advanced
14 aqua$.ab,ti. 55338 Advanced
15 cycl$.ab,ti. 869432 Advanced
16 aerobic.ab,ti. 62579 Advanced
17 strength$.ab,ti. 268677 Advanced
18 therap$.ab,ti. 2096049 Advanced
19 physiotherap$.ab,ti. 17436 Advanced
20 train$.ab,ti. 374146 Advanced
21 neuromuscular training.ab,ti. 250 Advanced
22 treadmill.ab,ti. 25619 Advanced
23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 4118759 Advanced
24 Osteoarthritis, Hip/ or Osteoarthritis, Knee/ 21491 Advanced
25 coxarthritis.mp. 98 Advanced
26 coxarthr$.ab,ti. 1644 Advanced
27 gonarthr$.ab,ti. 1098 Advanced

28 (knee$ adj3 pain).ab,ti. 6955 Advanced
29 (hip adj3 pain).ab,ti. 3697 Advanced
30 (degenerative joint? or degenerative cartilage).ab,ti. 2588 Advanced
31 osteoarthritis/ 33290 Advanced
32 (osteoarthr* or OA or 'osteo arthr*' or arthropath* or arthros$).ti,ab. 91174 Advanced
33 Hip Joint/ 24989 Advanced
34 Hip/ 11138 Advanced
35 hip$.ab,ti. 260568 Advanced
36 Knee/ 12882 Advanced
37 knee$.ab,ti. 107460 Advanced
38 knee joint/ or patellofemoral joint/ 48603 Advanced
39 24 or 25 or 26 or 27 or 28 or 29 31010 Advanced
40 30 or 31 or 32 102726 Advanced
41 33 or 34 or 35 or 36 or 37 or 38 371406 Advanced
42 40 and 41 40822 Advanced
43 39 or 42 54553 Advanced
44 randomized controlled trial.pt. 453975 Advanced
45 controlled clinical trial.pt. 92158 Advanced
46 (placebo or (standard adj3 care)).ab. 194944 Advanced
47 clinical trials as topic.sh. 182638 Advanced
48 random$.ab,ti. 822283 Advanced
49 trial$.ab,ti. 744520 Advanced
50 RCT.ab,ti. 12375 Advanced
51 44 or 45 or 46 or 47 or 48 or 49 or 50 1532587 Advanced
52 limit 51 to humans 1321908 Advanced
53 23 and 43 and 52 4030 Advanced
54 Individualised.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,
protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3772 Advanced
55 Stratif$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol
supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
121870 Advanced
56 Individualized.mp. 29333 Advanced
57 (personalised or personalized).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword
heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22169 Advanced
58 individualisation.mp. 536 Advanced
59 individualization.mp. 3701 Advanced
60 personal$.mp. 333548 Advanced
61 Tailored.mp. 34695 Advanced
62 Tailoring.mp. 9291 Advanced
63 subgroup analysis.mp. 14167 Advanced
64 subgrouping.mp. 892 Advanced
65 Predictor of response.mp. 1243 Advanced

66 Predictors of response.mp. 2011 Advanced
67 stratification.mp. 41366 Advanced
68 stratified.mp. 72840 Advanced
69 personalization.mp. 1022 Advanced
70 personalisation.mp. 200 Advanced
71 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 539435 Advanced
72 53 and 71 187 Advanced
73 Hip pain/ or Knee pain.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 4960 Advanced
74 43 or 73 54597 Advanced
75 Knee Injuries/ or Patella/ or Knee Joint/ or Arthralgia/ 70894 Advanced
76 Hip pain/ or Hip Joint/ or Femoracetabular Impingement/ or Arthralgia/ 31897 Advanced
77 43 or 73 or 75 or 76 119563 Advanced
78 23 and 52 and 71 and 77 256 Advanced

Appendix 2: Reviewer's involvement

Action	Reviewer
Individualised exercise (IE)	
Development of search strategy	Khalid Yaseen
Initial search (2017)	Khalid Yaseen
Screening of titles and abstracts	Khalid Yaseen
Validation of screening of titles and abstracts	Burak Kundakci
Full-text screening	Khalid Yaseen
Validation of full-text screening	Burak Kundakci
Data extraction	Khalid Yaseen
Validation of data extraction	Burak Kundakci
Risk of bias assessment	Khalid Yaseen
Validation of risk of bias assessment	Burak/Ayah
Intervention description assessment	Khalid Yaseen
Validation of intervention description assessment	Ayah Ismail
Search update (2020)	Khalid Yaseen
Non-individualised exercise (NIE)	
Development of search strategy	Siew Li Goh
Initial search (2017)	Siew Li Goh
Screening of titles and abstracts	Siew Li Goh
Validation of screening of titles and abstracts	Siew Li Goh
Full-text screening	Siew Li Goh
Full-text screening to identify NIE studies	Khalid Yaseen
Search update (2020)	Khalid Yaseen
Data extraction of studies identified in NIE search update	Khalid Yaseen

Appendix 3: Data extraction tool (Example)

DATA EXTRACTION FORM

Date of review **:** 2/8/2018 **ID of reviewer:** KY

Title of article **:** Physical therapy vs internet-based exercise training for patients with knee osteoarthritis: results of a randomized controlled trial

Year: 2018. **Journal:** Osteoarthritis and cartilage (OARSI). **Volume**: 26. **Page**: 383–396.

Author(s): K.D. Allen et al.

A. Study characteristics

-

Country: USA Year: 2018 **Language: English**		
Funding: Public ☒ Commercial ☐ Unclear ☐ Others:		
Diagnosis made using: K/L grade ☐ **ACR** ☒ **Duration of pain** ☐ **Unclear** ☐ **Others:** Radiographic features		
Grouping:		
Group 1	Group 2	Group 3

Supervised physiotherapy.	Internet-based exercise training (IBET)	Waiting list.

Design: Parallel ☒ Crossover ☐ Others: Other types

Intervention duration: 12 months

Timing of follow-ups: 4 Months – 12 months

Outcome:

Primary1: WOMAC for pain

Secondary1 WOMAC for physical function (pf)

Secondary2: --

B. Participant Characteristics

Demographic	Group 1 (PT)	Group 2 (IBET)	Group 3 (WL)	Total
Number of participants	140	142	68	350
Number of withdrawals	11	30	5	46
Age (mean ± SD)	65.7 ± 10.3	65.3 ± 11.5	64.3 ± 12.2	65.3 ± 11.1
Male/ Female	42/98	42/100	15/53	99/251

C. Exercise Characteristics

Intervention	Type of Exercise	Duration	Indicator of individualization	Mode of delivery
Group 1: Supervised PT.	Strengthening, Stretching and aerobic.	12 months Frequency not specified	Not individualised	Supervised
Group2: Internet-based exercise training (IBET)	Strengthening, Stretching and aerobic.	At least 3 sessions per week. 12 months.	Exercise difficulty was tailored according to patients' pain severity, functional ability and level of physical activity. Patients get assigned to one of 7 of exercise difficulty levels.	Internet-based

Appendix 4: Quality appraisal tool

Please see the following page for full assessment criteria	Yes	No	Unclear	Comments
1. Was the randomisation procedure adequate?	☐	☐	☐	
2. Was the treatment allocation adequately concealed?	☐	☐	☐	
3. Were participants blinded to the intervention?	☐	☐	☐	
4. Were physicians blinded to the intervention?	☐	☐	☐	
5. Were outcome assessors blinded to the intervention?	☐	☐	☐	
6. Incomplete outcome data: Is the attrition rate <15%?	☐	☐	☐	
7. Are all pre-specified outcomes of interest reported in the pre-specified way?	☐	☐	☐	
8. Was intention-to-treat analysis used?	☐	☐	☒	
9. Were the treatment and control group similar at baseline?	☐	☐	☐	

Appendix 5: TIDeiR checklist

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	_____	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	_____	_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	_____	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	_____	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	_____	_____
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	_____	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	_____	_____

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	_____	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	_____	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	_____	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	_____	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	_____	_____

Appendix 6: List of excluded studies

Study	Reason for exclusion
(Hiyama et al., 2016)	Controlled but not randomized. The study compared Group-based exercise versus individualised exercise programs.
Replacement (Łyp et al., 2016)	Not controlled.
(Wood et al., 2016)	Exercise is not individualised within OA group.
(Williams et al., 2015)	Only protocol, complete trial report not available.
(Murphy et al., 2016)	Did not involve any form of exercise. Only general activity pacing.
(Foster et al., 2014)	Only protocol, complete trial report not available.
(Bossen et al., 2013a)	Did not involve any form of exercise. Only generic physical activity advice.
(Ageberg et al., 2013)	Controlled but not randomized
(Bossen et al., 2013b)	Did not involve any form of exercise. Only generic physical activity advice.
(Barker et al., 2013)	Pot arthroplasty rehabilitation. Not OA[1] patients.
(Hasegawa et al., 2013)	- No diagnosis for OA. Only knee pain patients. - No randomisation.

(Minor et al., 1989)	Exercise not individualised within OA group.
(Bennell et al., 2012)	Only protocol, complete trial report not available.
(Schepens et al., 2012)	Did not involve any form of exercise. Only general activity pacing.
(Rosa et al., 2012)	No randomisation
(Murphy et al., 2012)	Only protocol, complete trial report not available.
(Wright et al., 2011)	Predictors of response. Not RCT[2].
(Murphy et al., 2010)	- Did not involve any form of exercise. Only generic activity pacing program.
(Coulter et al., 2009)	- Did not involve any form of exercise. Only generic physical activity advice. - No randomisation
(Jenkinson et al., 2009)	Diet was individualised but exercise was not.
(Talbot et al., 2003)	Exercise is not individualised.
(Keays et al., 2015)	No randomisation.
(Deyle et al., 2005)	Exercise is not individualised.
(Allen et al., 2010).	Exercise is closely supervised but not individualised.
(Mason et al., 2011)	Exercise is not individualised.

(Read et al., 2011)	Exercise is not individualised.
(Hiyama et al., 2016)	Exercise is not individualised. Individualisation definition in this trial meaning the perception of exercise was delivered to each individual separately not in group. However the content of the exercise program is the same for all patients.
(Hay et al., 2006)	Exercise is not individualised.

[1]OA= Osteoarthritis.
[2]RCT= Randomised Controlled Trial.

Appendix 7: Adaptations to exercise program

The study by De rooji et al (2017) categorised adaptations to exercise program into the following three sections:

1- General adaptations:

- Use the results of a maximum or symptom-limited exercise test to calculate the individual aerobic exercise intensity in patients with cardiac problems. (If the patient is using beta blockers, the exercises should be based on the results of the maximum or symptom-limited exercise test with beta blocker use). The optimized exercise zone can be calculated using the Karvonen formula, which calculates the exercise heart rate as a percentage of the heart rate reserve (the difference between the maximum heart rate and the heart rate at rest), added to the resting heart rate. Patients should start with 2 weeks of exercise at 40%–50% of their VO2 max then gradually raise the training intensity from 50% to 80% of their VO2 max or VO2 reserve.
- Base the exercise intensity on a percentage of the maximum capacity expressed in watts or METs and/or a Borg RPE-scale (6–20) (24) if the patient's heart rate does not rise sufficiently during the maximum or symptom-limited exercise test (see Load intensities expressed in various training load

measures as reported by the American College of Sports Medicine, Pollock et al 1990 (25)).

- Continue monitoring and observing of the individual response of the patient and the way they tolerate the exercise load, and check whether the patient shows any signs of excessive strain.
- Perform interval training for patients in poor physical condition instead of continuous aerobic training.
- Perform dynamic instead of static strength exercise to prevent high blood pressure
- Reduce the training intensity in warm climatic conditions.

2- Coronary disease:

- Pain in the chest during exercise: Terminate exercise, ask patient to sit down in chair, wait for reduction of angina. If no reduction: ask if patient uses nitro spray, if yes: apply nitro spray. If no reduction, confer with medical specialist.
- Insufficient knowledge of the disease and exercise options and/or fear of exertion:

    A- Provide information about disease and exercise options.

B- Coaching to improve confidence in exercising; i.e. consider starting at lower exercise intensity and give positive rewarding feedback.

3- Heart failure:

- see coronary disease
- Prolong the warming-up and cooling-down sessions to decrease the risk of cardiac decompensation.
- Be careful with Valsalva Manoeuvres, changing body position such as a supine to standing position because of reduced capacity to adapt blood pressure.
- Start at lower exercise intensity and consider high intensity interval training (HIIT). Avoid a rapid increase in the peripheral resistance training in patients with heart failure, as this increases the afterload strongly and the risk of decompensation. For improving muscle strength, start with 2 weeks on 30%–40% of 1RM and then gradually increase the resistance from 50% to 70%–80% of 1RM.
- Start with resistance training to reduce peripheral blood pressure and cardiac load before aerobic training
    - Monitor recovery to normal ADL functioning within 3-4 hours after exercise. In case of reduced recovery, reduce training intensity.

The study by Saccmanno et al (2016) categorised adaptations to exercise program into the following three sections:

A. Varus knee (medial tibio-femoral compartment)

- Manual therapy;
- Stretching of the following muscles: psoas, hip external rotators, medial flexors, biceps femoris and gastrocnemius;
- Isometric exercises for quadriceps, biceps femoris and tensor fascia lata;
- Isotonic exercises with elastic resistance (tubing) for quadriceps, biceps femoris and tensor fascia lata;
- Proprioceptive rehabilitation.

B. Valgus knee (lateral tibio-femoral compartment)

- Manual therapy;
- Stretching of the following muscles: psoas, medial flexors, biceps femoris, tensor fascia lata and gastrocnemius;
- Isometric exercises for quadriceps, hip adductors and medial flexors;
- Isotonic exercises with elastic resistance (tubing) for quadriceps, hip adductors and medial flexors;
- Proprioceptive rehabilitation.

C. Patello-femoral osteoarthritis

- Manual therapy;
- Stretching of the following muscles: psoas, hip external rotators, medial flexors, biceps femoris, tensor fascia lata and gastrocnemius;
- Isometric exercises for quadriceps;
- Isotonic exercises in closed kinetic chain for quadriceps with elastic resistance;
- Proprioceptive rehabilitation.

Appendix 8: Delphi ethical approval

Dear Khalid Yaseen

Ethics Reference No: 362-1907 **– please always quote**	
Study Title: The Optimal Strategies to Individualise Exercise Interventions for Hip and Knee Osteoarthritis Patients: A Delphi Survey.	
Chief Investigator/Supervisor: Dr Michelle Hall, Assistant Professor, Arthritis Research UK Pain Centre/Division of Physiotherapy, School of Health Sciences	
Lead Investigators/student: Khalid Yaseen, PhD Student, Physiotherapy, School of Health Sciences	
Other Key investigators: Professor Mike Doherty, Head of Department and Director of Clinical and Epidemiological Research, Prof Zhang Weiya, Professor of Epidemiology, Dr Abhishek Abhishek, Clinical Associate Professor of Rheumatology, Rheumatology, Orthopaedics and Dermatology, School of Medicine	
Proposed Start Date: 20/07/2019	**Proposed End Date:** 31/12/2019

Thank you for submitting the above application which did not require a full research ethics committee meeting review because it is aiming to generate a consensus of opinion around current practice which will inform for planning future research. In this case the participants are not the subject of the research but are providing expert opinion to inform. The following documents were received:

- FMHS REC Application and supporting documents version 1.0: 09.07.2019

These have been reviewed and are satisfactory and the study has been given a favourable opinion.

Yours sincerely



Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix 9: Delphi invitation letter

[Dear participant],

My name is Khalid Yaseen, and I am a PhD student at the University of Nottingham, UK.

My PhD research is exploring how best to individualise exercise interventions for people with knee or hip osteoarthritis (OA) and supervised by Dr Michelle Hall, Prof Michael Doherty, Prof Weiya Zhang and Dr Abhishek.

Individualised exercise interventions are internationally recommended for people with knee or hip OA but details on how exercise should be individualised are sparse.

As a recognised expert in the field of OA and or exercise, I would like to invite you to participate in a Delphi survey to consider what are the most important factors or patient characteristics that should be considered when individualise exercise for people with OA.

The Delphi survey will take place between March and May 2019.

In the first round, you will be asked to generate a list of factors or patient characteristics, which you feel, are the most important things to take into consideration when individualising exercise. The responses from the first round will inform subsequent rounds where you will be asked to vote (agree/disagree) with the statements generated. Further rounds of voting will continue until there is agreed consensus for a final list of statements. It is anticipated that no more four rounds will be required and each round may take 10-15 minutes of your time.

To acknowledge your contribution, all participants who complete all stages of the Delphi exercise will be invited as co-authors of any future publication of the results.

I fully appreciate your time is always at a premium but I would be very grateful if you would agree to participate in this survey. Please contact me if you have any questions about the survey.

Best wishes

Khalid Yaseen
PhD student
School of health sciences, physiotherapy division, University of Nottingham
Room A24, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB.

Appendix 10: Full list of stakeholders meetings opinion statements.

First meeting's opinion statements
1- Co-morbidity and age shouldn't exclude people from exercise.
2- Presence of co-morbidity may impact each of the following: • The type and intensity of exercise program • Education about exercise benefits (exercise can be beneficial for OA and the co-morbidity as well). • Exercise prescription should be focused on empowering patients and giving them belief in their own abilities. • Exercise should be performed within acceptable safety measures.
3- Water-based exercise is recommended exercise for people with high BMI.
4- Safe exercise should be specifically considered for people with high risk of falling.
5- In presence of musculoskeletal pain elsewhere, exercise can be prescribed to improve all affected areas not only OA joint.
6- During education and exercise prescription, additional time should be given to those with lower learning abilities.
7- Exercise prescription should include alternatives to when the patient is having pain flare-ups.

8- Sessions should be a “two-way” learning process. Therapists should teach patients how to deal with pain and what is the difference between the OA pain and normal exercise aches. Also, therapists should listen carefully to what patients has to say about their personal experience.
9- It should be explained that exercise may not completely eliminate pain and patients should still exercise even if pain presents within acceptable limits.
10- Therapists should measure baseline abilities and set goals using objectives measures (e.g. Pedometer and Dynamometer).
11- Subjective measures for tiredness and ability to exercise should be considered
12- Exercise should start from the current ability of patient and progress gradually.
13- Patient’s preferences should be considered. Options of exercise can be provided and patients should choose what think is enjoyable and achievable. Also, preferences regarding settings of exercise (in groups or alone, in gym or at home).
14- Therapists should be able to signpost patients to relevant exercising groups.
15- Therapists and patients can structure an individualised SMART (Specific, Measurable, Attainable, Relevant and Timely) goals.
16- Set motivational strategies according to patient’s preferences:

• Role model • Small achievable goals according to preferences
17- Special consideration should be given to known behavioural change strategies for exercise prescription according to patient's needs.
18- Therapists should try to understand the social factors that affect the patient's adherence to exercise.
Second meeting's statements
1- The rheumatology team recommended giving a lot of attention to frailty rather than age. I was suggested using recognised measures for frailty to help structure exercise programs accordingly.
2- In regards to patients with high BMI they recommended prescribing swimming programs if feasible.
3- Meeting attendees agreed that pain is an important measure for individualising exercise and is the most important symptom for patients.
4- For those who are complaining of pain elsewhere in addition to their OA complaint it was recommended using mind body exercises as part of the treatment.
5- The rheumatology team recommended giving special consideration to fatigability of patients' in the process of individualising exercises.

6- Aerobic exercise was suggested for those with fatigue problems.
7- It was recommended to give special attention to measuring and treating balance for patients' safety.
8- Patients' previous experience with exercise and physiotherapy should be considered when taking history.
9- Therapists should be able to signpost patients to relevant exercising and support groups.
10- It was also suggested to discuss time constraints and adapt types of exercise in a way that suits patients' lifestyle.

Appendix 11: Invitation letter

17th FEB. 2020

Dear,

Invitation for participation

According to our records you have kindly participated in previous studies carried out by Academic Rheumatology and have agreed to be contacted about future studies. We would like to invite you to take part in a study that aims to test the acceptability of an individualised exercise intervention for people with painful knee OA.
Individualised exercise interventions are recommended for people with knee or hip OA but details on how exercise should be individualised are sparse. This study will look at how this can be done.

This research is led by Khalid Yaseen, a PhD student at the University of Nottingham, UK. This project is supervised by Dr Michelle Hall, Prof Michael Doherty, Prof Weiya Zhang and Dr Abhishek.

The study will take place between February and May 2020. If you agree to take part you will attend for an assessment (an examination of your knee, some measures of function and some questionnaires) and have a programme of individualised exercise and education about your knee pain prescribed for you. You will have between 4 and 6 visits in total.

Please find enclosed a Participant Information Sheet with further details of this study. If you would like to take part, then please complete the reply slip and return it to the research team in the self-addressed envelope provided.
If you would like to ask any questions about the research before you return the reply slip, then you can contact the research team on 0115 823 1759 OR 07588268937 and someone will be happy to help with additional information. Once the research team has received your reply slip, you will be contacted to check you are suitable for the study and arrange for your first visit.

Thank you for considering participation in this research.

Yours sincerely,

Mr Khalid Yaseen

Khalid M Yaseen

Appendix 12: Invitation Reply Slip

In order to confirm your eligibility to participate in this study we would like to ask you few questions. Before you respond to these questions, please kindly study the information on the participant information sheet attached

1- Are you interested in participating in the **Individualised Exercise for Knee Osteoarthritis Study?**

Yes, I am interested in participating the study ☐

No, I am not interested in participating in the study ☐

2- Did you have **knee pain** for most of the days in the **past month**?

Yes, I had knee pain in the past month ☐

No, I did not have knee pain in the past month ☐

3- Did you have **knee pain** for at least 3 months in the **past year**?

Yes, I had knee pain in the for 3 months in the past year ☐

No, I did not have knee pain in the for 3 months in the past year ☐

Please contact Mr. Khalid Yaseen on 0115 823 1759 OR 07588268937 if you would like to find out more about this study.





……..x……....

If you have answered yes to the first question to the question above please confirm your contact details:

Address……..…….

……..…….

……..…….

Phone number……..……..

Preferred day/time for phone calls……..

Email..……..……..

Appendix 13: Patient information sheet

We would like to invite you to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. One of our team will go through the information sheet with you and answer any questions you have. Please take time to read this carefully and discuss it with others if you wish. Please do not hesitate to ask if anything is not clear.

Why have I been invited to take part?

We are sending you this information sheet as our research team has identified that you suffer from knee arthritis and might be appropriate for this study.

You should read this information sheet in detail before deciding whether you wish to take part or not.

Do I have to take part?

No. It is up to you to decide if you want to take part in this research. We will describe the study and go through this information sheet with you to answer any questions you may have. If you agree to participate, we will ask you to sign a consent form and will give you a copy to keep. However, you would still be free to withdraw from the study at any time, without giving a reason and without any negative consequences, by advising the researchers of this decision.

1. What will happen to me if I take part?

A researcher will contact you to go over the information sheet, explain the procedures, and go through a pre-screening with you to check if it is appropriate and safe for you to participate. If you agree to take part in the study, you will be asked to attend a number of visits at the Clinical Sciences Building at Nottingham City Hospital.

The study will involve providing some education materials about osteoarthritis and you will also be educated to perform a number of therapeutic exercises in the physiotherapy gym. This exercise program will be tailored according to your needs. You will be asked to perform exercises regularly at home and you will be seen by a physiotherapist for 4-6 sessions. The first session will be in Rheumatology Department in City hospital while the follow up sessions can be wither in the department or home visits (the therapist comes to your home for follow up assessments).

Assessments will be undertaken at an initial appointment and last appointment. The assessments include muscle strength tests, joint functionality, pain level and a number of questionnaires regarding your knee pain and arthritis.. At the end of the study you will also be asked to fill a patient satisfaction questionnaire.

If you inform us that you are happy to take part in this study, you will be contacted by the research team to arrange an initial morning appointment

to attend the Nottingham City Hospital. This initial appointment will take up to 2 hours. You will be given the opportunity to ask any questions you have about the study before being asked to sign a consent form. Follow-up visits may take 30-45 minutes and will all take place in the same site. You also have the option have the follow up sessions at home if you cannot attend to the City Hospital.

2. *Are there any risks in taking part?*

The types of exercises in this study, which is recommended by the National Institution of Health and Care for Excellence (NICE), are very safe. There is a small chance that it may initially increase your knee, hip or low back pain. This pain usually settles within just a couple days. We will monitor your pain levels on a weekly basis, and any unexpected or non-resolving pains. You will be advised to stop the exercises and contact your GP, should this happen.

3. *Are there any benefits in taking part?*

The exercise regimen that you will be given has the potential to improve your knee pain and function, and if you persist with the exercises it may benefit your current knee problem long-term. In addition, the results of this study will help us understand how we can best individualise exercises for different people. This may subsequently lead to better management of people with painful knees and OA.

4. *Will my time/travel costs be reimbursed?*

Participants will not receive an inconvenience allowance to participate in the study. Travel expenses will be offered for any visits incurred as a result of participation. If required a taxi can be arranged to collect you and take you home after the study. However, if you wish you may also use the free service provided by MediLink buses.

5. *What happens to the data provided?*

We will follow the required ethical and legal practice, and all information about you will be handled in confidence.

If you join the study, some parts of your medical records and data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant, and we will do our best to meet this duty.

All information which is collected about you during the research will be kept **strictly confidential,** stored in a secure and locked office, and on a password-protected database. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security), and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data).

We would like your permission to use anonymised data in future studies, and to share our research data (e.g. in online databases) with other researchers in other Universities and organisations both inside and outside the European Union. This would be used for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. All personal information that could identify you will be removed before information is shared with other researchers or results are made public. Data sharing in this way is always anonymised (so that you could not be identified).

6. What will happen if I don't want to carry on with the study?

Your participation is voluntary, and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw, we will no longer collect any information about you or from you. However, if you withdraw then the information collected so far cannot be erased as we are not allowed to tamper with study records and this information may have already been used in some analyses and may still be used in the final study analyses.

7. Who will know that I am taking part in this research?

All information collected about you during this research would be kept strictly confidential. Any imaging and electronic data will be anonymised with a code as detailed above. All such data are kept on password-protected databases sitting on a restricted access computer system and

any paper information (such as your consent form, contact details and any research questionnaires) would be stored safely in lockable cabinets in a swipe-card secured building and would only be accessed by the research team.

Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx/

Designated individuals of the University of Nottingham may be given access to data for monitoring and/or audit of the study to ensure we are complying with guidelines.

With your consent, we will keep your personal information on a secure database in order to contact you for future studies.

8. What will happen to the results of the research?

We hope that the results of this study will lead to a better understanding of the best way to individualise exercise advice for people with knee OA. It will help to guide future management of this common type of arthritis. Results from the study will be submitted for publication in scientific and medical journals and presented at medical and scientific meetings. We will also provide you with a summary of the eventual results if you wish.

9. Who has reviewed this study?

All research involving people is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Faculty of Medicine and Health Sciences Research Ethics Committee.

10. Who is organising and funding the research?

This study is organised by members of staff in Academic Rheumatology, a department of the University of Nottingham based at the City Hospital. The facilities are provided by The University of Nottingham.

Appendix 14: Consent form

Title of Study: Individualised Exercise Package for Knee Osteoarthritis Patients: Acceptability Study

REC ref: *(to be added after approval given)*

Name of Researcher: Khalid Yaseen

Name of Participant:	**Please initial box**
1. I confirm that I have read and understand the information sheet version number 1 dated 18th November 2019 for the above study and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.	☐
3. I understand that relevant sections of data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. -	☐
4. I understand that information about me recorded during the study will be made anonymous before it is stored. It will be uploaded into a secure database on a computer kept in a secure place. Data will be kept for 7 years after the study has ended and then destroyed. -	☐
5. **Optional**: I agree that the research data collected about me may be stored and used in possible future research during and after 7 years, and shared with other researchers including those working outside the University.	☐
6. I understand that the tests or procedures are carried out for research only and not for clinical diagnostic purposes. However, if the study investigator should feel it necessary	☐

to inform my GP of my participation in the study, or of an adverse event or abnormal test result, I understand I am giving my consent to do so.

7. I have not been a subject in any other research study in the last three months which involved: taking a drug; being paid a disturbance allowance; having an invasive procedure (e.g. blood sample >50ml) or exposure to ionising radiation.

8. I voluntarily agree to take part in the above study.

Name of Participant	Date	Signature
_____	_____	
Name of Person taking consent (if different from Principal Investigator)	Date	Signature
_____	_____	
Name of Principal Investigator	Date	Signature

Appendix 15: Functional exercise



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Functional exercise

Step-Ups to the side

Stand sideways on a step with one foot hanging over the edge of the step.

Slowly bend your knee allowing your other foot to brush the floor.

Repeat _____ times.

Perform _____ sets



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Functional exercise

Step-Downs

Stand on one leg on a step facing down.

Slowly lower yourself by bending your knee.Return to starting position. Keep the knee pointing straight ahead.

Repeat _____ times

Perfrom _____ sets



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Functional exercise

Sit-to-stand

Lean forwards slightly and stand up tightening your buttock muscles.
Keep your head and chest up and knees pointing straight ahead.
Sit down slowly pushing your hips backwards.

Repeat _____ times.

Perform _____ sets



©The Hygenic Corporation

Functional exercise:

Mini squat with theraband

Begin by holding the theraband in both hands near your hips. Stand on the middle of the band with both feet.
Perform minisquat, keeping back and elbows straight. Hold for 5 seconds and slowly return.
Keep your back straight and knees pointing forward.

Use _____theraband

Repeat _____ times

Perform _____ sets



©PhysioTools Ltd

Functional exercise.

Bridge

Lie on your back with legs bent.

Squeeze your buttock muscles and roll your pelvis off the floor.Lift hips off the floor, Hold for 3 seconds

Slowly return to the starting position.

Repeat _____ times

Perform _____ sets



©PhysioTools Ltd

Functional exercise

Wall squats

Stand leaning with your back against a wall and your feet about 20 cm from the wall.

Slowly slide down the wall until your hips and knees are at right angles.
Hold for 10 seconds.
Only slide down as far as you can control the movement.
Keep knees pointing straight ahead.

Return to starting position.

Repeat _____ times

Perform _____ sets



©PhysioTools Ltd

Functional exercise

Step-Ups

Stand in front of a stair step.

Step up slowly with one leg leading and then lower slowly.
Keep knee pointing straight ahead.
Use the wall or stair rail to balance if needed.

Repeat _____ times

Perform _____ sets

Appendix 16: Aerobic Chair-based exercise



©Glasgow Caledonian University

Feet: Feet on the floor

Upper Body: Double shoulder shrugs

Time 30 secs



©Glasgow Caledonian University

Feet: Feet on the floor

Upper Body: Alternating elbow bends

Time: 30 seconds



©Glasgow Caledonian University

Feet: Feet on the floor

Upper Body: Roll hand around each other at shoulder height

Time: 30 seconds



©Glasgow Caledonian University

Feet: Feet on the floor

Upper Body: Lift both arms out to side with elbows bent

Time: 30 seconds



©Glasgow Caledonian University

Feet: Feet on the floor

Upper Body: Climb a rope

Time: 30 seconds



©Glasgow Caledonian University

Feet: Heel tap with each foot. Repeat.

Upper Body: Elbows bent - open and close arms

Time: 30 seconds



©Glasgow Caledonian University

Feet: Feet on the floor

Upper Body: Crawl - swimming stroke

Time: 30 seconds



©Glasgow Caledonian University

Feet: Lift each knee. Repeat.

Upper Body: Punch alternate arms upward

Time: 30 seconds



©Glasgow Caledonian University

Feet: Heel tap with each foot. Repeat.

Upper Body: Pull arms upward in a rowing motion

Time: 30 seconds



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Sit.

Bend and straighten your ankles.

Time: 30 seconds



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Sit on a chair with the soles of your feet on the floor.

Lift one leg into the air and touch the heel of your foot with the opposite hand. Repeat with the other leg.

Time: 30 seconds



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Sit on a chair with the soles of your feet on the floor.

Lift one leg into the air and clap your hands together under the leg. Return the leg to the starting position. Repeat with the other leg.

Time: 60 seconds



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Sit up straight on a chair with the soles of your feet on the floor.

Lift one foot off the floor and take it to the side, with heel leading. Return to the starting position. Repeat with the other leg.

Time: 60 seconds



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Heel raise

In standing, push up on toes.

Time 30 secs



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In standing, lift alternate knees to hip height.

Time: 60 seconds



©PhysioTools Ltd

In standing.

Squeeze your buttocks and bring one leg behind you keeping your knee straight. Do not lean forwards or let your lower back arch.

Alternate legs. Time 60 secs



©PhysioTools Ltd

In standing
Lift your leg sideways and bring it back keeping your trunk straight throughout the exercise.

Alternate legs. Time 60 secs



©PhysioTools Ltd

From standing - mini squat
Slowly bend your hips and knees, try to push your bottom back as if you were sitting down. Stand up tightening your buttock muscles.

Time 60 secs

Note. Knees and feet point in the same direction.

Appendix 17: Physiotherapy outpatient satisfaction questionnaire: Items scoring and subscales.

1. My therapist gave me confidence that I was going to get better
2. I was not always seen promptly for my treatment sessions
3. I did not have confidence that the therapist knew what (s)he was doing
4. I should have got a better result from the treatment I was given in this department
5. I expected the treatment would help relieve my pain
6. My therapist did not listen to what I had to say
7. I have made a full recovery as a result of treatment
8. I did not have any of my treatment sessions cancelled
9. I expected the treatment would get me better
10. The treatment helped me at the time but the effect did not last
11. My therapist gave me encouragement and praise
12. I was not happy to be left to work on my own during the session
13. I expected the treatment would cure my problem
14. The treatment was too rushed
15. I am completely satisfied with all aspects of my visit to the physiotherapy department
16. The therapist explained my condition to me in great detail
17. I did not think treatment would be able to help me
18. I was able to choose the appointment times for treatment
19. The treatment has helped me in some ways but I am not completely better
20. My therapist did not seem interested in me
21. It was important for me to see the same therapist throughout my treatment
22. The treatment was tailored to my needs
23. I was able to ask the therapist about anything connected with my treatment
24. I had to wait a long time to get my first appointment for treatment
25. The treatment sessions were too short
26. The treatment has not helped me at all
27. My therapist put me at ease and was very kind to me
28. The therapist did not answer all my questions
29. I got on very well with my therapist
30. Treatment sessions were too infrequent to get any benefit
31. I am now completely pain free as a result of treatment
32. I was made aware of my responsibilities in managing my condition as a result of treatment
33. I did not have the undivided attention of the therapist during my treatment
34. I am completely satisfied with the treatment I received in this department
35. I have regained full mobility as a result of treatment
36. I was able to contact the department for help if I had any further problems after discharge
37. The quality of service I received in this department could have been better
38. The treatment was fully explained to me

*__Items__: Item statements are presented in the order with which they appear in the questionnaire. However, the style of the questionnaire is not reproduced here.

__Scoring__:

5-point Likert scale: 5 = strongly agree; 4 = agree: 3 = not sure; 2 = disagree; 1 = strongly disagree

__Reversed scoring on items__: 2,3,4,6,10,12,14,17,19,20,24,25,26,28,30,33,37 (5 = 1, 4 = 2, 2 = 4, 1 = 5)

__Items in each of the 6 Subscales__: Expectations: 1,5,9,13,17; Therapist: 11,20,21,27,29,32,; Communication: 3,6,16, 23,28,38; Organisation: 2,8, 12,14,25,30,33,36; Clinical outcome: 7,10,19,26,31,35; Satisfaction: 4,15,18,22,24,34,37.

Appendix 18: International Physical Activity Questionnaire - Short Form (IPAQ-SF)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**.

Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week**

☐ No vigorous physical activities - ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**.

Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis?
Do not include walking.

_____ **days per week**

☐ No moderate physical activities - ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don’t know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking - ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don’t know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don’t know/Not sure

This is the end of the questionnaire, thank you for participating.

Appendix 19: Illness Perception Questionnaire (IPQ-R)

ILLNESS PERCEPTION QUESTIONNAIRE (IPQ-R)

Name..... *Date*.....

YOUR VIEWS ABOUT YOUR ILLNESS

Listed below are a number of symptoms that you may or may not have experienced since your illness. Please indicate by circling *Yes* or *No*, whether you have experienced any of these symptoms since your illness, and whether you believe that these symptoms are related to your illness.

	I have experienced this symptom *since my illness*			This symptom is *related to my illness*	
Pain	Yes	No	_____	Yes	No
Sore Throat	Yes	No	_____	Yes	No
Nausea	Yes	No	_____	Yes	No
Breathlessness	Yes	No	_____	Yes	No
Weight Loss	Yes	No	_____	Yes	No
Fatigue	Yes	No	_____	Yes	No
Stiff Joints	Yes	No	_____	Yes	No
Sore Eyes	Yes	No	_____	Yes	No
Wheeziness	Yes	No	_____	Yes	No
Headaches	Yes	No	_____	Yes	No
Upset Stomach	Yes	No	_____	Yes	No
Sleep Difficulties	Yes	No	_____	Yes	No
Dizziness	Yes	No	_____	Yes	No
Loss of Strength	Yes	No	_____	Yes	No

We are interested in your own personal views of how you now see your current illness.

Please indicate how much you agree or disagree with the following statements about your illness by ticking the appropriate box.

	VIEWS ABOUT YOUR ILLNESS	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
IP1	My illness will last a short time					
IP2	My illness is likely to be permanent rather than temporary					
IP3	My illness will last for a long time					
IP4	This illness will pass quickly					
IP5	I expect to have this illness for the rest of my life					
IP6	My illness is a serious condition					

	VIEWS ABOUT YOUR ILLNESS	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
IP7	My illness has major consequences on my life					
IP6	My illness does not have much effect on my life					
IP9	My illness strongly affects the way others see me					
IP10	My illness has serious financial consequences					
IP11	My illness causes difficulties for those who are close to me					
IP12	There is a lot which I can do to control my symptoms					
IP13	What I do can determine whether my illness gets better or worse					
IP14	The course of my illness depends on me					
IP15	Nothing I do will affect my illness					
IP16	I have the power to influence my illness					
IP17	My actions will have no affect on the outcome of my illness					
IP18	My illness will improve in time					
IP19	There is very little that can be done to improve my illness					
IP20	My treatment will be effective in curing my illness					
IP21	The negative effects of my illness can be prevented (avoided) by my treatment					
IP22	My treatment can control my illness					
IP23	There is nothing which can help my condition					
IP24	The symptoms of my condition are puzzling to me					
IP25	My illness is a mystery to me					
IP26	I don't understand my illness					
IP27	My illness doesn't make any sense to me					
IP28	I have a clear picture or understanding of my condition					
IP29	The symptoms of my illness change a great deal from day to day					
IP30	My symptoms come and go in cycles					
IP31	My illness is very unpredictable					
IP32	I go through cycles in which my illness gets better and worse.					
IP33	I get depressed when I think about my illness					
IP34	When I think about my illness I get upset					
IP35	My illness makes me feel angry					
IP36	My illness does not worry me					
IP37	Having this illness makes me feel anxious					
IP38	My illness makes me feel afraid					

CAUSES OF MY ILLNESS

We are interested in what you consider may have been the cause of your illness. As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your illness rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your illness. Please indicate how much you agree or disagree that they were causes for you by ticking the appropriate box.

	POSSIBLE CAUSES	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
C1	Stress or worry					
C2	Hereditary - it runs in my family					
C3	A Germ or virus					
C4	Diet or eating habits					
C5	Chance or bad luck					
C6	Poor medical care in my past					
C7	Pollution in the environment					
C8	My own behaviour					
C9	My mental attitude e.g. thinking about life negatively					
C10	Family problems or worries caused my illness					
C11	Overwork					
C12	My emotional state e.g. feeling down, lonely, anxious, empty					
C13	Ageing					
C14	Alcohol					
C15	Smoking					
C16	Accident or injury					
C17	My personality					
C18	Altered immunity					

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

The most important causes for me:-

1. _____
2. _____
3. _____

Appendix 20: Ethical approval of acceptability study

University of Nottingham
UK | CHINA | MALAYSIA

Faculty of Medicine & Health Sciences Research Ethics Committee
Faculty Hub
Room E41, E Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham, NG7 2UH
Email: FMHS-ResearchEthics@nottingham.ac.uk

11 February 2020

Dr Michelle Hall
Assistant Professor
Division of Physiotherapy and Rehabilitation Sciences
The University of Nottingham
Room B78, Clinical Sciences Building
Nottingham University Hospitals, City Campus
Hucknall Road
NG5 1PB

Dear Dr Hall

Ethics Reference No: 479-1912 – **please always quote**	
Study Title: Individualised Exercise Package for Knee Osteoarthritis Patients: Acceptability Study	
Chief Investigator/Supervisor: Dr Michelle Hall, Assistant Professor, Physiotherapy and Rehabilitation Sciences, School of Health Sciences.	
Lead Investigators/student: Mr Khalid Yaseen, PhD Student, Physiotherapy and Rehabilitation Sciences, School of Health Sciences.	
Other Key investigators: Professor Michael Doherty, Head of Department and Director of Clinical & Epidemiological Research, Weiya Zhan, Professor of Epidemiology, Dr Abhishek Abhishek, Clincial Associate Professor of Rheumatology, Division of Rheumatology, Orthopedics and Dermatology, School of Medicine	
Proposed Start Date: 01/2020	**Proposed End Date:** 31/07/2020

Thank you for submitting the above application and the following documents were received:

- FMHS REC Application form and supporting documents version 1.0: 18/11/2019

These have been reviewed at the meeting on 13 December 2019 and the project has been given a favourable opinion.

A favourable opinion has been given on the understanding that:

1. The protocol agreed is followed and the Committee is informed of any changes using a notice of amendment form (please request a form).
2. The Chair is informed of any serious or unexpected event.
3. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Delphi study approval:

University of Nottingham
UK | CHINA | MALAYSIA

Faculty of Medicine & Health Sciences
Research Ethics Committee
Faculty Hub
Room E41, E Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham, NG7 2UH
Email: FMHS-ResearchEthics@nottingham.ac.uk

19 July 2019

Khalid Yaseen
PhD Student
Division of Physiotherapy and Rehabilitation Sciences
The University of Nottingham
Room A24, Clinical Sciences Building
Nottingham University Hospitals, City Campus
Hucknall Road
NG5 1PB

Dear Khalid Yaseen

Ethics Reference No: 362-1907 **– please always quote**	
Study Title: The Optimal Strategies to Individualise Exercise Interventions for Hip and Knee Osteoarthritis Patients: A Delphi Survey.	
Chief Investigator/Supervisor: Dr Michelle Hall, Assistant Professor, Arthritis Research UK Pain Centre/Division of Physiotherapy, School of Health Sciences	
Lead Investigators/student: Khalid Yaseen, PhD Student, Physiotherapy, School of Health Sciences	
Other Key investigators: Professor Mike Doherty, Head of Department and Director of Clinical and Epidemiological Research, Prof Zhang Weiya, Professor of Epidemiology, Dr Abhishek Abhishek, Clinical Associate Professor of Rheumatology, Rheumatology, Orthopaedics and Dermatology, School of Medicine	
Proposed Start Date: 20/07/2019	**Proposed End Date:** 31/12/2019

Thank you for submitting the above application which did not require a full research ethics committee meeting review because it is aiming to generate a consensus of opinion around current practice which will inform for planning future research. In this case the participants are not the subject of the research but are providing expert opinion to inform. The following documents were received:

- FMHS REC Application and supporting documents version 1.0: 09.07.2019

These have been reviewed and are satisfactory and the study has been given a favourable opinion.

Yours sincerely

Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix 21: Good Clinical Practice (GCP) training certificate

NIHR | National Institute for Health Research

CERTIFICATE OF ACHIEVEMENT

Khalid Yaseen

has completed the course

Introduction to Good Clinical Practice (GCP) eLearning

March 10, 2020

Modules Completed:

Introduction to Research in the NHS and other settings

Good Clinical Practice and Standards in Research

Study Set-up and Responsibilities

Informed Consent

Data Collection and Documentation

Safety Reporting

Summary

This course is worth 4 CPD points.