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EFFECTIVENESS OF INTERNET-BASED EXERCISES AIMED AT TREATING KNEE OSTEOARTHRITIS (iBEAT-OA): A RANDOMIZED CLINICAL TRIAL

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Abstract

Importance

Osteoarthritis is a prevalent, debilitating and costly chronic disease for which recommended first-line treatment is underused.

Objective

To compare the effect of digital treatment for knee osteoarthritis via app versus routine self-management in a randomized, parallel-group clinical trial.

Design

A 6-week randomised controlled trial (iBEAT-OA) started in winter 2018.

Setting

Primary care.

Participants

551 participants, 45 years or older, with a diagnosis of knee osteoarthritis from an existing primary care database or from social media advertisements, were invited.

Intervention

The intervention (n=48) and control group (n=57) conformed to first-line knee osteoarthritis treatment. For intervention group, treatment was delivered via a smartphone application. The control group received routine self-management care.

Main outcome and measures

Primary outcome at 6 weeks was change from baseline in self-reported pain during the last seven days, reported on a Numerical Rating Scale (NRS, 0-10, 0 no pain, 10 worst pain), compared between the two groups. Secondary outcomes included two physical functioning scores, hamstring and quadriceps muscle strength, Sleep assessment, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Pittsburgh Sleep Quality Index (PSQI), General health questionnaire (MSK-HQ), Inflammatory markers on ultrasound (synovial fluid, synovial hypertrophy and hypervascularity) and quantitative sensory testing (QST).

Results

48 participants in the intervention group (mean age 65.2, 70.8% female, 30.4 BMI) and 57 participants in the control group (age 68, 64.9% female, 31.9 BMI) completed this study with no notable demographic difference between groups. The intervention group showed a greater NRS pain score decrease at follow-

up than the control group (between-group difference -1.5 [95%CI, -0.8 to -2.2; P<0.001]. Similarly, the 30-second sit to stand test (30CST) and Timed Up and Go test (TUAG) improved more in the intervention group, 3.4 (95%CI, -2.2 to -4.5) and -1.8 (95%CI, -0.5 to -3.0), as did the WOMAC subscales for pain, stiffness and physical function (-1.1 [95%CI, -0.2 to -2.0], -1.0 [95%CI, -0.5 to -1.5], and -3.4 [95%CI, -0.7 to -6.2]). The magnitude of within-group changes in pain and function outcomes in the intervention group corresponded to medium to very strong effects. There was no between-group difference seen in actigraphy sleep data, PSQI, MSK-HQ, QST and sonographic features of knee OA.

Conclusions and relevance

Digitally delivered evidence-based first-line OA treatment is superior to routine self-managed care as usual and can be given without harming people with osteoarthritis. Effect sizes observed in the intervention group correspond to clinically important improvements.

Publications and Presentations

Publications:

- Gohir SA, Greenhaff P, Abhishek A, Valdes AM. Evaluating the efficacy of Internet-Based Exercise programme Aimed at Treating knee Osteoarthritis (iBEAT-OA) in the community: A study protocol for a randomised controlled trial. *BMJ Open*. Published online 2019. doi:10.1136/bmjopen-2019-030564
- Gohir SA, Abhishek A, Kelly A, Valdes A. A Randomised Controlled Trial Evaluating the Efficacy of Internet-based Exercises Aimed at Treating Knee Osteoarthritis (iBEAT-OA) [abstract]. *Arthritis Rheumatol.* 2020; 72 (suppl 10).
- Gohir SA, Eek F, Kelly A, Abhishek A, Valdes AM. Effectiveness of internet-based exercises aimed at treating knee osteoarthritis: a randomized clinical trial. JAMA Netw Open. 2021;4(2):e210012. doi:10.1001/jamanetworkopen.2021.0012

In Press:

- Gowler, P; Turnbull, J; Shahtaheri, M; Gohir, S; Kelly, T; McReynolds, C; Jun , Y; Fernandes, G; Zhang, W ; Doherty, M; Walsh, D; Bruce, H; Valdes, A; Barrett, D; Chapman, V. Analgesic Potential of Soluble Epoxide Hydrolase Inhibition for Osteoarthritis Pain (2021) *Arthritis and Rheumatology.*
- Jiang, T; Yang, T; Zhang, W; Doherty, M; Zhang, Y; Wei, J; Sarmanova, A; Hall, M; Yang, Z; Li, J; Fernandes, G; Obotiba, A; Gohir, S; Courtney, P; Aliabadi, P; Zeng, C; Lei, G.H. Prevalence of

Ultrasound-Detected Knee Synovial Abnormalities in a Middle-Aged and Older General Population - the Xiangya Osteoarthritis Study (2021) *Osteoarthritis and Cartilage*

Presentations:

- Gohir S, Abhishek A, Kelly A, Valdes A. A Randomised Controlled Trial Evaluating the Efficacy of Internet-based Exercises Aimed at Treating Knee Osteoarthritis (iBEAT-OA) [abstract]. *Arthritis Rheumatol.* 2020; 72 (suppl 10). *Oral Presentation in ACR Convergence 2020.*
- Gohir S, Greenhaff P, Abhishek A, Kelly A, Valdes A. A Randomised Controlled Trial Evaluating the Efficacy of Internet-based Exercises Aimed at Treating Knee Osteoarthritis (iBEAT-OA). *Oral Presentation and Runner up prize winner in Sue Watson Oral Presentation Competition 2020*.
- Gohir S, Greenhaff P, Abhishek A, Kelly A, Valdes A. A Randomised Controlled Trial Evaluating the Efficacy of Internet-based Exercises Aimed at Treating Knee Osteoarthritis (iBEAT-OA). *Oral Presentation in Trauma and Orthopaedic Conference, Queen's Medical Centre 2020.*
- Gohir S, Greenhaff P, Abhishek A, Kelly A, Valdes A. A Randomised Controlled Trial Evaluating the Efficacy of Internet-based Exercises Aimed at Treating Knee Osteoarthritis (iBEAT-OA). *Oral Presentation in Annual BRC Meeting 2019*.

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PhD student contribution to this project

Dr Ana M. Valdes was responsible for conceptualising and securing funds for this project. SG (author) has done the following in this project:

- Played a pivotal role in designing this RCT under the supervision of Dr Ana M. Valdes and other supervisors, especially selecting secondary outcome measures and how they were going to be assessed.
- Written protocol for this study.
- Submitted protocol to sponsor (University of Nottingham) and National Institute for Health Research (NIHR) for its approval.
- Facilitated the approval by responding to their queries and gained approval.
- Liaising with Joint Academy (JA)- company that provided online exercise intervention and ensured that the online portal was fully functional.
- Completed good clinical practice and phlebotomy (blood withdrawal) training. Completed occupational health checks to run this project.
- Dealt with logistics of this project, including recruiting participants, supervising any participants recruitment issues, adhering to inclusion/exclusion criteria, assist with logistics of storing samples and data.
- Conducting research sessions (initial visit and 6-week follow up visit) with participants and collecting data from participants with the help of a research nurse (Tony Kelly).
- Data acquisition, analysis, and interpretation of data.

- Writing this thesis under the supervision of research supervisors

COVID-19 impact statement

Owing to the COVID-19 lockdown in the United Kingdom in March 2020, the following happened:

- The study had to be stopped due to lockdown and according to national and university COVID-19 lockdown guidelines. This resulted in 27 participants not completing their face-to-face follow-up visits at 6 weeks intervals, and the study did not reach its intended statistical power.
- The research team had to scan and shift completed questionnaires so that data can be accessed/analysed remotely.
- This led to delays in accessing and calculating data.
- As a result of COVID-19, this thesis was submitted electronically.

Abbreviations

ARUK	Arthritis Research United Kingdom
BMI	Body Mass Index
CI	Chief Investigator
ci	Confidence Interval
CPM	Conditioned pain modulation
ES	Effect Size
GCP	Good Clinical Practice
iBEAT-OA	Randomized controlled trial (RCT) on Internet-Based Exercises Aimed at Treating Knee Osteoarthritis (This study)
ICC	Intraclass correlation co-efficient
ICF	Informed Consent Form
JA	Joint Academy
JSN	Joint Space Narrowing
K/L	Kellgren and Lawrence system for classification of osteoarthritis of knee
MRI	Magnetic Resonance Imaging
MSK-HQ	The arthritis Research UK Musculoskeletal Health Questionnaire
MSK-USS	Musculoskeletal ultrasound scan

MVC	Maximum Voluntary Contraction
NHS	National Health Service
NICE	National Institute for health and clinical excellence
NRS	Numerical rating scale
NUH	Nottingham University Hospital Trust
OA	Osteoarthritis
PA	Posterior-Anterior
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSQI	Pittsburgh sleep quality index
QST	Quantitative Sensory Testing
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Sleep Efficiency
SF	Synovial fluid
TIB	Time in Bed
TS	Temporal Summation
TST	Total Sleep Time

TUAG	Time up and go test
USGA	Ultrasound-guided aspiration
WASO	Wakefulness occurring After defined Sleep Onset
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
30CST	30-second sit to stand test

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Chapter 1 Introduction

1.1 Osteoarthritis

Osteoarthritis (OA) is one of the most common causes of disability in the elderly population, and most individuals suffering from OA are managed in the primary care setting (Sharma, 2021, Valdes and Stocks, 2018). In the United Kingdom, approximately 8.75 million people have painful joints attributed to OA (Walker et al., 2017). The musculoskeletal calculator estimated that 4.11 million people in England had knee OA in 2019 (VersusArthritis, 2019). The National Joint Registry (NJR) has reported 312,167 primary knee procedures from 1st Jan 2017 to 31st Dec 2019, and these numbers were presented in their latest 17th Annual report published in September 2020 (Registry, 2020).

Osteoarthritis is defined as "*A group of overlapping disorders with different aetiologies but similar biologic, morphologic and clinical outcomes. The disease processes affect articular cartilage, subchondral bone, synovium, capsule and ligaments. Ultimately, cartilage degenerates with fibrillation, fissures, ulceration and full-thickness loss of joint surface.*" (Cooper et al., 2014)

The changes to the articular cartilage of the involved joint happen secondary to imbalances between anabolic and catabolic processes swayed by biomechanical forces as well as disturbances in autocrine, paracrine and endocrine modulation at a cellular level, leading to a fluctuation in normal tissue turnover within the joint (Herrero-Beaumont et al., 2009).

OA is an age-related painful joint condition typically affecting knees, hips and hands. It is accompanied by structural changes on radiographs (Figure 1-1), resulting in loss of function and ultimately ending in joint replacement.

Although the prevalence and incidence of OA certainly increase with age, it is not an inevitable consequence of ageing. Pain and disability are variables present in individuals suffering from osteoarthritis. While pain and disability can be quite debilitating for some, structural changes can progress without symptoms in others (Cisternas et al., 2016).

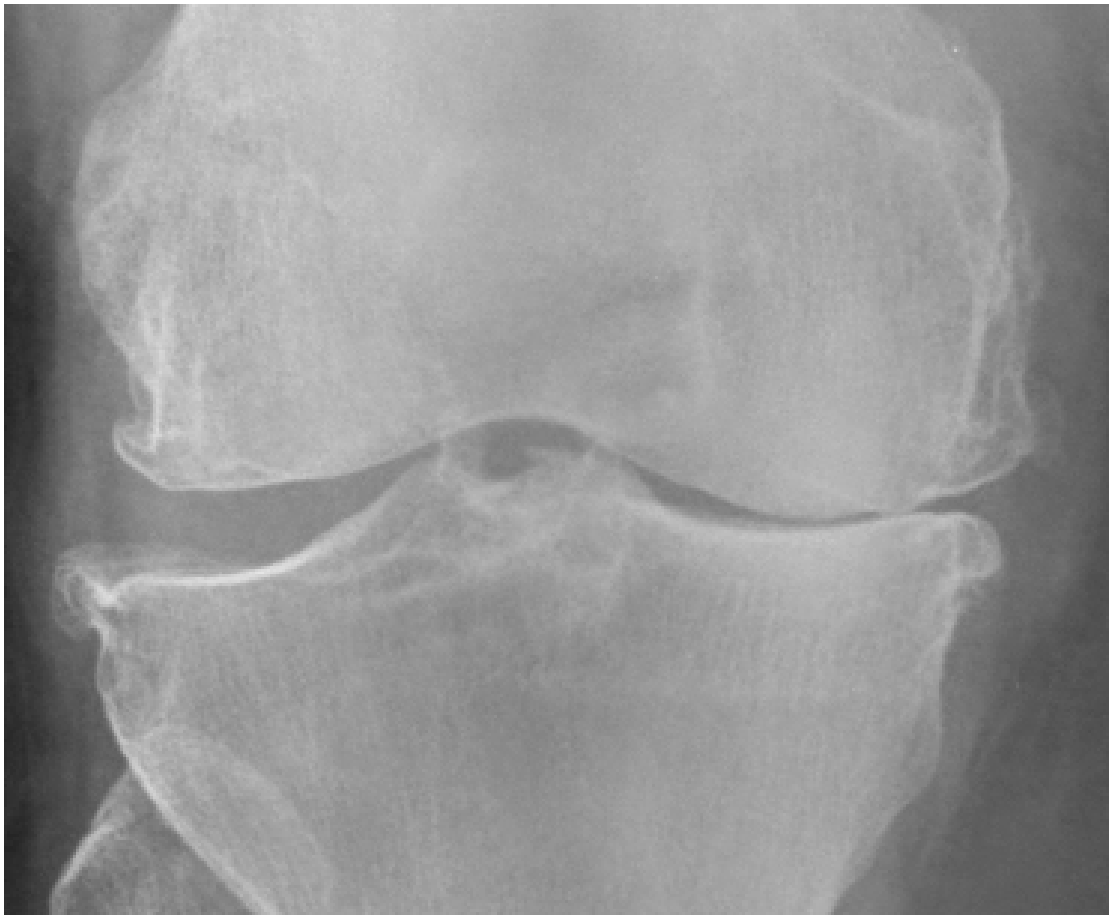


Figure 1-1: Posteroanterior radiograph showing medial tibiofemoral joint space narrowing, marginal osteophytes at all four sites (Courtesy of Prof. Michael Doherty).

1.2 Knee Osteoarthritis and its epidemiology

Knee OA is a common form of arthritis globally (Felson, 1996, Neogi and Zhang, 2013, Reynaud et al., 2020). Knee OA has doubled in prevalence since the mid-20th century (Wallace et al., 2017). A multisite peripheral joint pain cross-sectional study has analysed pain in hands, hips, knees or feet and reported that knee pain was the most prevalent single site (Finney et al., 2017). Some of these individuals are referred to allied health professionals, including physiotherapists and occupational therapists, to manage their OA, while others are referred to rheumatologists and orthopaedic surgeons. There is an increasing burden on secondary care for joint replacements, and National Joint Registry (NJR) has reported 103,617 primary knee replacement procedures done in 2019, published in their latest report (Registry, 2020). On average, total knee replacement (TKR) was costing £7458 per patient, including five years of subsequent care in 2012 (Dakin et al., 2012). It is difficult to obtain the recent cost of TKR in NHS setup; however, private hospitals are charging anything between £11,400 - £15,400 per TKR, which excludes the cost of physiotherapy post-surgery (EuroTreatMed, 2020). This should give us a rough estimation as to how much we are spending on TKR procedures.

1.3 Risk Factors for Knee Osteoarthritis

Large population studies have identified several risk factors associated with knee pain and osteoarthritis development and progression. They are broadly categorised into systemic and mechanical factors. Systemic factors increase

the susceptibility of an individual to develop osteoarthritis, and mechanical factors interfere with joint integrity and function.

1.3.1 Systemic Risk Factors

There are multiple systemic risk factors reported by a recent meta-analysis (Bastick et al., 2015) which linked OA to increasing age (Riddle et al., 2009, Riddle et al., 2012, Miyazaki et al., 2002, Muraki et al., 2012, Schouten et al., 1992), female gender (Collins et al., 2014, Ledingham et al., 1995), black ethnicity (Kopec et al., 2013), insulin-like growth factor (IGF-1) (Hartley et al., 2020), metabolic syndrome (MetS) (Yoshimura et al., 2012), genetic influence (Warner and Valdes, 2016) and single-nucleotide polymorphisms (SNPs) (Wang et al., 2016). Metabolic syndrome (MetS) consists of factors including an increased body mass index (BMI), hypertension (HTN), hyperlipidaemia and Diabetes Mellitus (DM) (Courties et al., 2017).

1.3.1.1 Hypertension

Systemic Hypertension (HTN) is postulated to cause subchondral ischaemia, which can compromise nutrient exchange in the articular cartilage and trigger bone remodelling (Zhuo et al., 2012, Ching et al., 2021). Several studies have shown that OA is more common among hypertensive patients (Veronese et al., 2018, Herrero-Beaumont et al., 2017). A recent meta-analysis included two cohort studies and six cross-sectional studies (n=9762), and they reported that HTN was significantly associated with higher radiographic knee OA risks of 2.01 (95% CI, 1.26–1.77, I^2=0%, P for heterogeneity <.412) and symptomatic

knee OA risks of 1.49 (95% CI, 1.26–1.77, I^2=0%, P for heterogeneity <.412) (Zhang et al., 2017). They reported no publication bias in included studies. This meta-analysis had few limitations. The use of anti-hypertensive drugs was not described in the included studies, which might have offered a further explanation of the relationship. Also, due to the inclusion of observational studies, confounding factors were inherited, and the risk estimates might be underestimated or exaggerated.

1.3.1.2 Dyslipidaemia

Dyslipidaemia itself and leading to secondary arteriosclerosis can also induce deregulation of cellular lipid metabolism in joint tissues, resulting in OA's initiation (Engström et al., 2009, Zhuo et al., 2012).

A recent systematic review and meta-analysis including 39 cross-sectional, ten cohort and nine case-control studies reported that the association between knee OA and dyslipidaemia was confirmed with increased risk of dyslipidaemia (OR 2.27, 95% CI 1.33 to 3.89) (Baudart et al., 2017). They removed the heterogeneity of the studies assessed by I^2 index, and the results were not changed by removing most heterogeneous studies. However, this data after removing heterogeneous studies was not shown in this study. They could not integrate confounding factors such as age, HTN, BMI, smoking, physical activity and the impact of statin treatment. Although there is an association between dyslipidaemia and OA, however, the pathophysiological explanation of this relationship is not clearly defined. Studies on mice showed that dietary cholesterol intake increased spontaneous cartilage damage in mice (Gierman

et al., 2014). Increased LDL levels promoted ectopic bone formation and synovial inflammation in the mice OA model (de Munter et al., 2016). Further studies are required depicting the pathophysiological relationship between OA and dyslipidaemia, and in the interim, screening and management of cardiovascular comorbidities should be focused on.

1.3.1.3 Diabetes Mellitus

Diabetes mellitus (DM) has a pathogenic effect on OA through two major pathways (Veronese et al., 2019). The first one is described as oxidative stress. DM leads to local accumulation of advanced glycation end-products, contributing to a toxic intra-articular environment that facilitates OA pathogenesis (Zhuo et al., 2012, Veronese et al., 2019). This leads to the overproduction of pro-inflammatory cytokines and advanced glycated end products (AGEs) in joint tissue (Veronese et al., 2019). The second pathogenic effect is low-level chronic inflammation resulting from chronic hyperglycaemia and insulin resistance (Veronese et al., 2019) which may affect the local joint or whole body.

DM has been associated with adverse structural changes such as increased cartilage volume loss and bone marrow lesions (BMLs) over two years in the knee (Davies-Tuck et al., 2012). Another cohort study showed that hyperglycaemia was associated with increased risk of knee OA (RR 2.2, 95% CI 1.4–3.6), but after adjustment for BMI, the strength of association diminished (RR 1.4, 95% CI 0.9–2.4) (Engström et al., 2009). This may be due to the fact that hyperglycaemia, being a marker of insulin resistance, metabolic syndrome and type 2 diabetes, is highly positively correlated with obesity (Srikanthan et

al., 2016) and thus, the association with hyperglycaemia might simply have been reflecting its association with BMI, a well-known strong risk factor for OA. Another cohort study with over 20 years' follow-up reported diabetes to be associated with increased risk of hip or knee OA (HR 2.1, 95% CI 1.1–3.8) (Schett et al., 2013). They wanted to determine if DM was an independent risk predictor for severe OA and recruited 927 men and women aged 40-80 years. They concluded that DM predicts the development of severe OA independent of age and BMI. This was the first study that showed that DM predicts severe OA independent of age, sex, and BMI and provided longitudinal and cross-sectional evidence for an independent association between DM and OA.

1.3.1.4 Obesity

A strong relationship between obesity and knee OA has been reported by several studies (Chen et al., 2020, Kulkarni et al., 2016). It has been proposed that metabolic risk factors and low-grade systemic inflammation, which often is increased in obesity, could contribute to OA (Scanzello, 2017, Robinson et al., 2016, Büchele et al., 2018, Marshall et al., 2019). The prevalence of hand OA in the obese population suggests that its mechanism of action is not entirely biomechanical. Obesity is assumed to induce the expression of proinflammatory factors and degradative enzymes, leading to the hindrance of cartilage matrix synthesis and subchondral bone remodelling (Zhuo et al., 2012). These pro-inflammatory factors and degradative enzymes are known as adipocytokines which are found in adipose tissue (Sowers and Karvonen-Gutierrez, 2010, Belluzzi et al., 2017) in the obese population. These adipocytokines (type of cytokines) are leptin, resistin and adiponectin. Leptin,

adiponectin, and resistin are assumed to sway osteoarthritis through direct joint degradation or control of local inflammatory processes (Sowers and Karvonen-Gutierrez, 2010). Leptin is generally higher in obese individuals, and Leptin expression has been directly associated with the degree of cartilage degeneration (Stannus et al., 2015, Huang et al., 2016).

Additionally, the combined effect of leptin and proinflammatory cytokines (interleukin-6 [IL-6] and tumour necrosis factor-alpha [TNF-α]) have been reported in cartilage degradation (Wang and He, 2018). Adiponectin has surfaced as a controller of immune reactions and inflammatory arthritis (Tilg and Moschen, 2006, Neumann et al., 2011), but its role in OA and cartilage degradation is divisive and, in many aspects, poorly known. A study collected cartilage and blood samples from 35 male OA patients undergoing total knee replacement surgery and reported that adiponectin is associated with, and possibly mediates, cartilage destruction in OA (Koskinen et al., 2011). They also noted that the amount of adiponectin released by OA cartilage ex-vivo also correlated positively with the production of inflammatory mediators such as nitric oxide (NO) and interleukin-6 (IL-6) and with the matrix-degrading enzyme matrix metalloproteinase 3 (MMP-3). These findings indicate that adiponectin is linked with cartilage matrix degradation and has a role in the pathogenesis or as a biomarker in OA. Resistin levels in both the serum and synovial fluid are higher in OA, and rheumatoid arthritis patients than in healthy subjects and resistin levels are much higher in serum than in synovial fluid, indicating that the mechanism may be more endocrine than just local degradation in the joints (Zhao et al., 2019). In human cartilage, resistin induces the expression of proinflammatory factors such as degradative enzymes, leading to the inhibition

of cartilage matrix synthesis, perhaps by binding to Toll-like receptor 4 and the adenylyl cyclase-associated protein 1 receptor. These receptors then ultimately activate the p38 mitogen-activated phosphate kinase, protein kinase A–cyclic AMP, nuclear factor-κB, and C-enhancer-binding protein β signalling pathways; however, the precise role of resistin in the pathogenesis of OA needs to be studied further (Zhao et al., 2019).

The mechanical aspect of obesity is covered under section 1.3.2.1.

1.3.1.5 Metabolic Syndrome (MetS)

A strong correlation between BMI and MetS could cause problems in separating the effects of these risk factors in the multivariate models. A cohort study calculated the tolerance values for the multivariate models to determine the degree of collinearity between the independent variables (Engström et al., 2009). Multivariate statistics permit associations and effects between predictor and outcome variables to be adjusted for by demographic, clinical, and prognostic variables (simultaneous regression) (Shipe et al., 2019). When carrying multivariate statistics, it is essential to consider multicollinearity, which happens when predictor variables are highly correlated to each other, or assessing the same thing twice in a model (Menard, 2002, Shipe et al., 2019). This can artificially inflate or deflate the statistical significance associated with the model (Bursac et al., 2008). Multicollinearity is assessed statistically using two different methods: Tolerance and the variance inflation factor (VIF) (Vatcheva et al., 2016, Kim, 2019). Smaller tolerance values denote the presence of multicollinearity variables, and it is suggested that tolerance values below 0.20 should be regarded as potential collinearity problems (Menard,

2002). VIF values above 2.5 also suggest the presence of multicollinearity (Senaviratna and Cooray, 2019). A small tolerance value indicates that the variable under review is almost a perfect linear combination of the independent variables already in the equation and that it should not be added to the regression equation (Senaviratna and Cooray, 2019, Vatcheva et al., 2016, Dormann et al., 2013). All variables involved in the linear relationship will have a small tolerance (Midi et al., 2010). Some suggest that a tolerance value less than 0.1 should be investigated further (Kim, 2019). If a low tolerance value is accompanied by large standard errors and non-significance, multicollinearity may be an issue (Dormann et al., 2013).

When all covariates were assessed in the final model, tolerance for MetS was 0.79 (Engström et al., 2009). This means that 79% of the variance of MetS was unique for that variable, and all other independent variables could explain 21%. They concluded that BMI is not so closely linked to the MetS as one might expect.

Another cohort study recruited 24,430 and examined whether MetS was associated with the incidence of severe knee or hip OA (Monira Hussain et al., 2014). They reported that the cumulative number of MetS components, HTN and central obesity were associated with an increased risk of severe knee OA. They did not record medication for DM or lipid-lowering agents, which means that despite having altered DM or lipid profile in some participants, these participants were being classified as having normal serum measures, thus potentially leading to some biasness in the results.

1.3.1.6 Female gender

A recent meta-analysis (Silverwood et al., 2015) with eleven cohort studies assessed female gender as a potential risk factor, and it concluded that females are at higher risk of knee OA, with pooled OR 1.68 (95% CI 1.37–2.07). Some speculate this association may be due to lack of oestrogen in the post-menopausal stage and may be responsible for higher prevalence of knee OA in females (J. et al., 1999, Samanta et al., 1993, Spector et al., 1994, Roman-Blas et al., 2009). Some studies suggested that taking oestrogen in the form of hormone replacement therapy offers protection against knee OA (J. et al., 1999, Samanta et al., 1993, Szoeke et al., 2006, Zhang et al., 2011a, Dawson et al., 2003, T. et al., 1990, Yuqing et al., 1998), however recent meta-analysis studies (Blagojevic et al., 2010, Silverwood et al., 2015) reported that this is not the case.

1.3.1.7 Hand osteoarthritis

Hand OA or Heberden's nodes diagnosed clinically was assessed as a risk factor by multiple cohort studies for knee OA. One meta-analysis (Silverwood et al., 2015) reported pooled OR of 1.30 (95% CI 0.90–1.87), and another meta-analysis (Blagojevic et al., 2010) reported pooled OR as 1.49 (95% CI 1.05, 2.10) indicating that hand OA may potentially be a risk factor for knee OA.

1.3.1.8 Depression

Depressive symptoms are frequent comorbidity of OA (Stubbs et al., 2016), and this meta-analysis reported the prevalence of depression to be 20% among the sufferers of OA. Depression may contribute to the severity and perseverance of OA symptoms (Cohen and Lee, 2015). Longitudinal studies have shown that symptoms of depression are predictive of changes in pain and functional limitations in OA (Collins et al., 2014, Riddle et al., 2011). Depression is associated with reduced physical performance and a prolonged sedentary lifestyle, leading to deconditioning of the body and greater BMI, which may inevitably result in greater structural derangements and OA disease progression (Demakakos et al., 2013, Beckwée et al., 2015). Most studies have focused on the effect of depression on OA symptoms but have not explored the association between depression and structural advancements on radiographs. Recent multi-site, prospective, observational cohort study, the first study to observe the relationship of depression and structural changes on knee radiographs, has studied their research participants over four years (Rathbun et al., 2017). They reported that depressed participants had a higher risk for joint space narrowing (JSN) progression from year 3 to year 4, although statistically, this was not significant between depressed and non-depressed participants. They reported that the impact of depression on the structural progression of knee OA on radiographs might be minimal or too small to detect. This study had few limitations; however, the most remarkable limitation was matching and the small overall outcome frequencies (166 individuals in the depression group and only 120 individuals who had radiographs in year 4). This might have reduced the statistical power and the ability to detect

differences in structural progression. Although there was no association between depression and structural advancement of knee OA on radiographs, however same study group reported in their other study that there was a dose-response relationship between depression and pain, indicating that OA knee pain increased significantly with increasing persistence of depressed mood (Rathbun et al., 2018). A recent meta-analysis has reported that depression was indirectly correlated with Charlson comorbidity index, polypharmacotherapy and BMI (Solmi et al., 2019), and these factors affect OA indirectly due to depression.

1.3.1.9 Psychological, social and other factors

One's pain experience is ascertained by a complex interaction of biological, psychological, and social factors (Gatchel et al., 2007, Allen et al., 2009, Somers et al., 2009). One example is the combined effect of depression and pain-related self-cognitions such as low self-efficacy and high catastrophizing are associated with worse pain perception and reduced functioning among OA sufferers (Tighe et al., 2019, Cheng et al., 2018). Social factors such as lack of support and/or stress can predict worse outcomes of OA (Wylde et al., 2019, Brembo et al., 2017). The degree of knee pain and disability symptoms in OA patients appears to be linked with various aspects, including structural changes, peripheral and central pain processing mechanisms, and psychosocial factors such as corpulence, culture and demographics (Helminen et al., 2016).

Unspecified pain elsewhere in the body reported by patients has been reported by two studies (Jinks et al., 2008, Ingham et al., 2011) and linked with increased knee pain. The first study was a prospective cohort study of 2982 participants from North Staffordshire, UK, who assessed their participants over three years (Jinks et al., 2008). Their response rates of questionnaire surveys were 77% (baseline) and 75% (follow-up). They reported that widespread pain as a predictor of the onset of knee pain had OR of 1.47 (95%CI 1.14 - 1.89) compared with no pain. Another study was a cohort study of knee pain undertaken on 2156 participants in North Nottinghamshire and studied these participants for over 12 years (Ingham et al., 2011). They reported that pain at other sites of the body, specifically the back pain (HR 1.41; 95% CI 1.21, 1.64) or hip pain (HR 1.57; 95% CI 1.31, 1.90), were significantly associated with the incidence of knee pain as reported by earlier studies (Jinks et al., 2008, Croft et al., 2005).

One Danish study has reported that low income or “blue collar” socioeconomic status are correlated with the development of knee pain in female participants (Jørgensen et al., 2011). They linked national register data about socio-demographic variables and OA hospital contacts to a cohort of 4.6 million Danish participants. Ratios of first OA hospitalisation rates (RRs) were calculated using Poisson regression. Women with relative household incomes of <50% or 50–75% of the average household income were at higher risk of knee OA (RR=1.10, 95% CI; 1.07-1.14 and RR= 1.12, 95% CI; 1.09- 1.14, respectively) than the reference group of women (corresponding to 75–125% of the average income). This correlation could not be established when household incomes of men were compared (<50% of the average household

income, RR= 0.75, 95% CI; 0.72–0.78 and 50–75% of the average household income, RR= 0.95, 95% CI; 0.92–0.97). Earlier mentioned study reported that psychosocial factors such as low education level and socioeconomic status/household income have a role which is reported non-significant but consistent associations between the progression of knee pain and these psychosocial factors (Jinks et al., 2008). They reported that among 923 participants with non-severe pain at baseline, 176 participants reported severe pain at three years follow-up and lower socioeconomic class was one of the independent predictors of progression to severe knee pain (OR 1.46, 95% CI, 0.88, 2.42).

A recent network analysis reported that income was associated with favourable health and lifestyle outcomes, namely education, quality of life, physical activity and adherence to the Mediterranean diet (Solmi et al., 2019) when the data of elderly North-American adults with or at risk for osteoarthritis was studied.

1.3.2 Mechanical Risk Factors

Mechanical factors are hypothesized to directly overload the knee joint or change its loading patterns in a way that some compartments of the knee joint take more load than other compartments.

1.3.2.1 Obesity

Obesity has been covered under systemic risk factors (section 1.3.1.4); however, the mechanical aspect of obesity is briefly covered here.

Obesity is associated with the excessive direct loading of the knee, predisposing to knee OA (Blagojevic et al., 2010, Silverwood et al., 2015). A meta-analysis (Muthuri et al., 2011) included 47 studies (446,219 participants) comprising 14 cohorts, 19 cross-sectional and 14 case-control studies. They reported that pooled OR for obesity was 3.91 (95%CI 3.32 – 4.56) and concluded that obesity is a risk factor for knee OA. A recent meta-analysis (Silverwood et al., 2015) reported pooled OR of the twenty-two studies as 1.98 (95% CI 1.57–2.20). A systematic review and meta-analysis consisting of 14 studies reported that overweight and obesity were significantly associated with higher knee OA risks of 2.45 (95% CI 1.88 -3.20) and 4.55 (95% CI 2.90 - 7.13), respectively (Zheng and Chen, 2015). The limitation of this meta-analysis was the small numbers of studies involved, with limited participants; however, they justified it by including high-quality clinical trials only, and therefore, generalising these results to all patients with OA should be performed with caution.

A recent retrospective study including 38050 participants meeting the criteria of OA, has done multivariate analyses (Johnston et al., 2020) and reported that patients with BMI > 40 Kg m^{-2} had an adjusted prevalence rate of OA that was nearly two times higher (21.9% vs 12.7%, respectively) than that of patients who were overweight (25-29.9 Kg m^{-2}). They had few limitations, one being one or more insurance claims based on the diagnosis of OA as one of the inclusion criteria. And the database did not have information on ethnicity, socio-economic status, or lifestyle habits such as alcohol intake, smoking habits, or eating and exercise habits, which could potentially confound the relationships observed in this study.

It was estimated that about 42% of knee OA in the UK might be avoided, should obesity be prevented (Zhang, 2010). This was calculated using population attributable risk percent (PAR%)=Pe(OR−1)/[Pe(OR−1)+1]×100%, where Pe is the percentage of exposure (in this case obesity). Given the odds ratio for obesity (OR=2.63, 95%CI 2.28–3.05) from the meta-analyses (Blagojevic et al., 2010), the PAR% would be 42%. The size of the benefit may vary from population to, and the impact increases with the increasing prevalence of obesity, with a prevalence of obesity of 60% (Zhang, 2010) the benefit due to the weight reduction would be 49% (95%CI 43–55%) of knee OA that could have been avoided.

1.3.2.2 Previous knee injuries

Previous knee injuries are associated with the early manifestation of OA, and several studies supported this proposition (Cooper et al., 2000, Gelber, 2000, Wilder et al., 2002, Toivanen et al., 2010, Zhang et al., 2011a, Kujala et al., 1995, McAlindon et al., 1996, J. et al., 1999, Hootman et al., 2003, Jinks et al., 2008, Ingham et al., 2011, Snoeker et al., 2020). A recent meta-analysis (Silverwood et al., 2015) confirmed that the pooled OR was 2.83 (95% CI 1.91–4.19). However, the extent of heterogeneity present between the findings reported was considerable (I^2 = 89.1%).

Another recent systematic review compared medial meniscus repair versus meniscectomy, including 13 studies with a mean duration of 33.5 and 47.2 months follow-up in the meniscal repair and partial meniscectomy groups, respectively (Ro et al., 2020). They reported prevalence of postoperative severe knee osteoarthritis (OR= 0.31, 95% CI, 0.17-0.54) favouring meniscal

repair. There were few limitations. They could not take into consideration the differences in the severity of knee osteoarthritis preoperatively, which could have affected the clinical and radiological outcomes after surgery. Additionally, they included only one type of meniscal repair (pullout suture technique through a transtibial tunnel). Therefore, the results of this study might not be generalised to other techniques of meniscal repairs (suture anchors or meniscal fixation devices). There is plenty of studies and systematic reviews assessing tibiofemoral OA post meniscal injuries and surgery; however, there is a lack of studies assessing OA in the patellofemoral joint. A recent study recruited 22 participants and evaluated them at a mean of 40 years post-meniscectomy using skyline radiographs (Pengas et al., 2019). They reported a correlation between meniscectomies and OA development demonstrated by an observed relative risk of 1.8 (95% CI 1.13–2.96). The small sample size is one of the limitations of this study; however, long term follow is the strength of this study.

Similarly, when reviewing anterior cruciate ligament (ACL) injuries, the chances of developing tibiofemoral joint OA in the affected knee after an ACL injury is 4 times higher than in the noninjured knee (Ajuied et al., 2014, Poulsen et al., 2019) and six times higher compared with a non-injured population (Snoeker et al., 2020). A recent cohort study that compared long term effects of ACL surgical (n=64) and non-surgical management (n=89) has observed these participants for 32-37 years (Kvist et al., 2020). Of the 89 participants allocated to non-surgical intervention, 53 remained nonsurgically treated, 36 had ACL surgery within 2 - 21 years after injury. This study reported that patients allocated to ACL surgery had a lower prevalence of tibiofemoral radiographic

OA at 32 to 37 years after injury compared with patients who managed ACL injury with non-surgical intervention. Unfortunately, they did not adjust their results for confounding factors such as sports participation or participation in other physical activities or other life events. These findings suggest that ACL injuries can increase the risk of developing OA knee; however, reconstructing ACL slightly reduces the chances of developing knee OA.

1.3.2.3 Overdoing activities

There is a school of thought that suggests that “overdoing” exercises or physical activities can also increase the risk of OA. Recent meta-analysis studies (Silverwood et al., 2015, Blagojevic et al., 2010) concluded an increased risk of OA in those individuals who exercise more regularly and intensely. These findings are based on high-quality cohort studies ranging from sixteen to twenty-one studies in each meta-analysis. One study suggested that consistent physical activity created the most significant risk (Felson et al., 1997). This meant that those with more varied exercise routines had less chance of developing knee OA. Another study found an increased risk of developing knee OA in those who ran 20 miles or more each week (Cheng et al., 2000). Similarly, studies recruiting sportsmen/women (soccer players, weight lifters) reported a higher risk in these groups (Driban et al., 2017, Freiberg et al., 2021, Spahn et al., 2015) which is associated with increased risk of injuries as a result of over-doing activities.

1.3.2.4 Certain professions

Those occupations which exert heavy physical workload are well known to be associated with knee OA. Kneeling was investigated and found to be significantly related to knee OA by some studies (Ingham et al., 2011, Zhang et al., 2011a, Kujala et al., 1995, Coggon et al., 2000, Cooper et al., 1994, D'Souza et al., 2008, Manninen et al., 2002, Sandmark et al., 2000, Tangtrakulwanich et al., 2006, Yoshimura et al., 2004). These studies suggested that jobs that required repeated kneeling can be classed as a risk factor for knee OA. Lifting was also associated with the knee OA (Dawson et al., 2003, Manninen et al., 2002, Coggon et al., 2000, D'Souza et al., 2008, Yoshimura et al., 2004, Lau et al., 2000, Ingham et al., 2011, Zhang et al., 2011a). Some other studies suggested that certain occupations exert constant pressure on the knee, leading to OA. These studies concluded that farming (Perry et al., 2020, Yucesoy et al., 2015, Parsons et al., 2020), construction work (Silverwood et al., 2015, Yucesoy et al., 2015) and physical education teaching (Mäkelä and Hirvensalo, 2015) were associated with the knee OA. A recent systematic review and meta-analysis conducted a sub-group meta-analysis of 23 occupations and found statistically significant higher odds of knee OA in 13 physically demanding jobs (Wang et al., 2020). Eight studies included in this meta-analysis assessed the relationship between agricultural, forestry and fishery industry work and risk of knee OA, respectively, which yielded incremental odds of 1.94 (95%CI: 1.56 to 2.42). They also reported that floor layers, bricklayers and carpenters had approximately 2.5 times increased odds of knee OA compared to sedentary workers. Farming, floor laying and bricklaying were associated with lower limb OA by another recent systematic

analysis and meta-analysis (Canetti et al., 2020). To summarise, it appears that individuals who are exposed to specific physical activities in their routine working lives are at an increased risk of developing knee OA.

1.3.2.5 Knee Malalignment

Knee malalignment is another mechanical risk factor leading to OA. A population-based cohort study of 1,501 participants, followed over a mean period of 6.6 years, found both valgus and varus alignment associated with an increase in the risk of development of knee OA (Brouwer et al., 2007). They reported that valgus alignment was associated with a borderline significant increase in the development of knee OA (OR = 1.54, 95% CI: 0.97-2.44), and varus alignment was associated with a 2-fold increased risk (OR 2.06, 95% CI: 1.28-3.32). It is postulated that malalignment, resulting from genetic, developmental, and/or traumatic factors, may lead to altered loading of the articular surfaces of the knee joint (Bruns et al., 1993, McKellop et al., 1994) and subsequent degenerative changes. A systematic review (Tanamas et al., 2009) concluded that malalignment is an independent risk factor for the progression of knee OA. Some high-quality radiographic (Brouwer et al., 2007, Sharma et al., 2001, Cerejo et al., 2002, Felson et al., 2004, Miyazaki et al., 2002) and MRI cohort studies (Cicuttini et al., 2004, Sharma et al., 2008) confirmed this association. These results were further supported by two high-quality cross-sectional studies (Birmingham et al., 2001, Issa et al., 2007). The results are consistent with biomechanical studies that show that varus and valgus alignment increase the medial and lateral load on the knee, respectively

(Bruns et al., 1993, McKellop et al., 1994). The most recent systematic review and meta-analysis reported that low quality of evidence was found for the odds of having malalignment in patients with knee OA compared to healthy control (van Tunen et al., 2018). They ruled out studies that compared knee alignment issues compared to the contralateral knee in the same individuals as opposed to the healthy control group. Also, it appeared that their focus was to assess for odds of having malalignment in patients with knee OA, however not OR of developing or progression of knee OA as reported by earlier systematic review (Tanamas et al., 2009). These findings suggest that malalignment results in a higher risk of progressive and degenerative changes. It is also possible that knee OA, including loss of cartilage and bone height, may lead to further malalignment, thus complicating this relationship of progressive OA due to malalignment or in fact, OA itself initiating malalignment and then secondary effect on the progression of knee OA. Future attempts should summarize comparison between contralateral knees in participants with mal-aligned knees versus comparison to healthy control group, should include all available data and investigate the importance of type of control (i.e. healthy controls or contra-lateral leg) in sensitivity analysis to also be able to include more longitudinal studies, so that we have conclusive evidence.

1.3.2.6 Weakness in knee extensors

Several studies have suggested that weakness in the knee extensor muscles contributes to incident knee OA (Bennell et al., 2013, Roos et al., 2011, Segal and Glass, 2021, Hassan et al., 2001, Heiden et al., 2009, Hurley et al., 1997, Lewek et al., 2004, Slemenda et al., 1997). The knee extensor muscles consist

of four muscles which are Vastus Lateralis (VL), Vastus Intermedius (VI), Vastus Medialis (VM) and Rectus Femoris (RF). One study suggested that all four muscles of knee extensors atrophy similarly in the elderly population (Trappe et al., 2001). Another study reported the atrophy of type 2 fibres in VL and associated it with OA compared to the controlled group (Nakamura and Suzuki, 1992). Atrophy of VM is associated with arthritis (Fink et al., 2007, Ikemoto-Uezumi et al., 2017), and greater VM cross-sectional area is associated with reduced knee pain and reduced medial tibial cartilage loss (Wang et al., 2012). There is no consensus as to which muscle weakness (VM or VL) is primarily responsible for knee OA in the participants, and there are conflicting results due to the heterogeneity of trial designs and assessment methods used in the studies.

One study suggested that greater quadriceps muscle strength protected individuals from symptomatic and painful knees; however, the radiographic progression of OA evolved as normal (Segal and Glass, 2021). A recent meta-analysis including five studies with 5,700 participants reported an increased risk of knee OA after 2.5-14 years follow-up in a mixed population of individuals with baseline knee extensor muscles weakness (Øiestad et al., 2015). They included heterogeneous populations, ranging from younger subjects with a knee injury to middle-aged persons with no previous knee injuries (Hootman et al., 2003), overweight individuals (Segal et al., 2009), and the elderly population (Slemenda et al., 1998). The results in different studies were compatible, both in men and women. They concluded that knee extensor muscle weakness is a general risk factor for knee OA across populations.

The mechanism by which weak knee extensor muscles act as risk factor for the development of knee OA is not fully understood (Øiestad et al., 2015). The knee extensors are thought to work as shock absorbents and stabilisers, and hence protecting the articular surfaces during loading activities and knee movements (Bennell et al., 2013). The weakness in the knee muscles is suggested to exert excessive mechanical stress on articular cartilage to induce a degenerative process (Palmieri-Smith and Thomas, 2009, Andriacchi et al., 2004). It remains to be proven if knee extensor muscle strengthening can reduce the onset or progression of knee OA (Øiestad et al., 2015); however, due to the beneficial effects on pain and function, muscle strengthening exercises are nevertheless recommended (Hochberg et al., 2012).

1.4 Pathology of Knee Osteoarthritis

1.4.1 Pathophysiology of Osteoarthritis

Different aspects of pathophysiology have been described in many OA pathogenesis models, and yet, we have an ambiguous concept of how these various aspects are interlinked and follow each other in a temporal sense (Weinans et al., 2012). A relevant question in this respect is what is damaged first: bone, cartilage or other peri-articular structures such as ligaments? It seems likely that this varies in different patients. Brandt et al. (2008) quoted the definition of OA as ‘OA should be considered a group of overlapping diseases with different aetiologies, but with similar biologic, morphologic, and clinical outcome. The disease process not only involves the articular cartilage but involves the entire joint, including subchondral bone, ligaments, capsule,

synovium, and periarticular muscles. Ultimately, the articular cartilage degenerates with fibrillation, fissures, ulceration, and full-thickness loss of the joint surface. Although they may be initiated by multiple factors, including genetic, developmental, metabolic, and traumatic, OA changes involve all tissues of the diarthrodial joint. When clinically evident, OA diseases are characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of inflammation without systemic effect (Brandt et al., 2008). While this definition of OA explains the processes involved but does not explain much about the pathophysiology of OA in the joint. OA can be heterogeneous in its origin and progression and can arise from different congenital, developmental, or acquired abnormalities that result in abnormal stress on the joint, such as abnormal joint shape, obesity, instability and/ or trauma. One example is that someone has congenital genu varum knee deformity, and over the years, this may lead to additional stress on the medial compartment of the knee joint, initiating or increasing the risk of knee OA.

Another example can be a footballer acquiring a complex meniscal injury leading to partial healing of the meniscus, abnormal knee joint loading, and additional stresses to that compartment of the knee joint, ultimately setting OA in the knee joint. OA represents a failure of the synovial joint, and any of the tissues of that organ may be first to fail; therefore, there can be many causes of OA. However, OA has no common pathophysiologic pathway, but only a common end-stage (articular cartilage degenerates with fibrillation, fissures, ulceration, and full-thickness loss of the joint surface) (Radin et al., 1991, Brandt et al., 2008). The wide range of risk factors and aetiologies that have been linked with OA, such as older age, obesity, meniscal derangements,

ligament sprain or tears, biomechanical factors such as joint shape and alignment, hormonal changes, metabolic disorders and genetic predisposition, indicate that there may be multiple underlying pathophysiological pathways leading to similar outcomes of joint destruction (Blagojevic et al., 2010, Johnson and Hunter, 2014, Deveza and Loeser, 2017).

While OA is characterised by the degradation and loss of articular cartilage, it is now widely appreciated that the processes leading to the pathological endpoint are active, dynamic, and involve all the tissues that comprise the joint organ, including bone cartilage, periarticular structures involving synovium and menisci. What was once described as a ‘wear and tear‘ process is now more appropriately referred to as ‘tear, flare and repair’, embodying the aetiological role of the initial biomechanical insult to the joint, the role of inflammation in pain and progression, and the mechanical adaptations of the joint tissues to compensate for the initial insult (Birrell et al., 2011).

The remodelling and production of new bone and the mechanical adaptations of the joint tissue often compensate for the initial insult that triggered the need for the joint to repair (Birrell et al., 2011). For some, however, the mediating effect of one‘s individual risk factors coupled with the overwhelming insult(s) or continued microtrauma in the joint means the joint cannot compensate effectively and then more commonly may associate with symptoms and loss of function, leading to decompensated OA or joint failure (Birrell et al., 2011).

1.4.2 Degenerative Changes in Cartilage

The primary changes with OA occur in the articular cartilage, followed by associated changes in the subchondral bone (Buckwalter et al., 2005, Loeser, 2010, Poulet et al., 2015). Recently, the primary cause of the symptomatic disease is considered to be degenerative changes in the subchondral bone (Goldring, 2000, Gomoll et al., 2010, Madry et al., 2010, Van Dijk et al., 2010), and new studies suggest it to be changes in cartilage-bone interface (Weinans et al., 2012, Findlay and Kuliwaba, 2016).

OA results from the failure of chondrocytes to maintain the balance between synthesis and degradation of extracellular matrix components (Buckwalter et al., 2006, Goldring and Goldring, 2007, Loeser, 2010, Rahmati et al., 2017). This extracellular matrix consists of two components. The first component is tissue fluid. The second is the framework of structural macromolecules consisting of type II collagen fibres, glycoproteins, proteoglycans and non-collagenous proteins, all formed in the appropriate amounts. They are organised into a highly organised molecular framework by the chondrocytes (Buckwalter et al., 2005, Rahmati et al., 2017). This collagen matrix forms cartilage and gives its tensile strength (Buckwalter et al., 2005). The imbalances in extracellular matrix components result in increased water content, decreased proteoglycan content, and weakening of the collagen network due to reduced synthesis of type II collagen and increased breakdown of pre-existing collagen (Buckwalter et al., 2005). Furthermore, there is an increased breakdown of chondrocytes. At first, increased proliferation of chondrocytes in the deeper layers of the cartilage and synthesis of matrix molecules can maintain the integrity of the articular cartilage (cartilage

remodelling-compensatory mechanisms). Still, eventually, changes in the extracellular matrix and loss of chondrocytes dominate, and osteoarthritic changes develop (Buckwalter et al., 2005).

The degradation of articular cartilage predominantly affects focal areas of cartilage subject to abnormal mechanical force, with other areas remaining intact. Progressive changes can then be observed in adjacent areas, until in advanced OA, more of the joint surface may be involved (Pritzker et al., 2006).

1.4.3 Degenerative Changes in Bone and Subchondral Region

In osteoarthritis, pathological changes of the subchondral bone, such as sclerosis, cyst formation and the presence of osteophytes, are typical. It shows an increase in bone volume density and reduced mineralisation content when bone from the individual with severe OA is analysed (Chen et al., 2015b). Interestingly, similar changes of the subchondral bone have been shown when bone samples from a population with minor cartilage damage are studied (Ding et al., 2001). Other studies reported that cartilage loss or further degeneration could be related to increased activity within the subchondral bone (Carlson et al., 1996, Dieppe et al., 1993, Matsui et al., 1997). There is an essential role of subchondral bone in evenly distributing the forces as a result of weight-bearing and impact, therefore protecting the cartilage from high peak stresses and damage (Weinans et al., 2012).

Most recent studies concentrate on the cartilage-bone interface and its interaction (Weinans et al., 2012, Findlay and Kuliwaba, 2016). There is evidence that the cartilage-bone interface is the key region in the development or progression of OA, even though the disease onset might have been triggered by an entirely different phenomenon such as ligament/meniscus trauma or a varus/valgus deformity. The cartilage-bone interface has a specific morphology and is consistent between different joints in many different species. This interface is a remnant of endochondral ossification, and it is often assumed that OA shows many aspects of endochondral ossification (Oegema et al., 1997), such as chondrocyte proliferation, hypertrophic chondrocytes in the deep cartilage zone, osteoclast infiltration and neovascularisation from the bone up to the deep cartilage zone. This process is accompanied by the formation of osteophytes and subchondral cysts (Glyn-Jones et al., 2015).

Bone marrow lesions (BMLs) represent further pathology of the subchondral bone in OA (Singh et al., 2019), a self-limiting process whose aetiology is not fully understood (Geith et al., 2020). This aetiology may be multi-factorial, and the most cited causes are repetitive subchondral bone microdamage and combined vascular alterations in the subchondral bone (Klement and Sharkey, 2019). The build-up of microdamage in bone is generally accepted as a result of repetitive loading, which surpasses the healing capacity of the bone tissue (Poulet et al., 2015). Patient factors such as mechanical alignment, reduced capacity to repair bone damage (i.e., post-menopause, smoking, vitamin D deficiency, etc.), and high BMI may further compromise the body's repair processes, thus increasing loss of cartilage which ultimately leads to increased subchondral bone stresses (Klement and Sharkey, 2019). From the vascular

perspective, areas of BML represent areas of outflow obstruction (Beckwée et al., 2015). This is coherent with previous studies that have portrayed areas of subchondral venous stasis and intraosseous hypertension in OA (Seah et al., 2012). Compromised vascular supply to the BML area in the setting of OA may predispose to their formation and further impede healing (Lee et al., 2009, Klement and Sharkey, 2019).

BMLs are a common finding in knee OA, defined on magnetic resonance imaging (MRI) as a focally increased signal in the marrow on fat-suppressed T2-weighted images (Felson et al., 2003, Yusuf et al., 2011, Nairn et al., 2020) and hypointense signal intensity on T1-weighted images (Geith et al., 2020). They are strongly predictive of persistent pain (O'Neill and Felson, 2018) and progression to arthroplasty (Felson et al., 2003, Scher et al., 2008). Although BMLs have been recognised on MRI for decades, Felson et al. (2001) were the first to document their clinical significance and correlation with patient symptoms. They performed a cross-sectional observational study on 401 patients with knee OA. They reported that BMLs were found in 272 of 351 (77.5%) patients with painful knees versus 15 of 50 (30%) patients without knee pain ($P < 0.001$). In addition, after adjustment for severity of radiographic disease, age, sex, BMI and presence of effusion, the presence of a BML (OR= 3.31; 95% CI, 1.54 to 7.41), and size of the BML (OR= 5.78; 95% CI, 1.04 to 111.11) remained independently associated with knee pain (Felson et al., 2001). A recent systematic review and meta-analysis reported an increase of ≥2 in Whole-Organ MRI scoring method (WORMS) BML score as a predictor of worsening knee pain after 15 months (OR: 3.2; 95% CI 1.5 to 6.8) (Sandhar et al., 2020). WORMS is a semi-quantitative counting method for multi-feature,

whole-organ assessment of the knee in osteoarthritis (OA) based on magnetic resonance imaging (MRI) findings (Peterfy et al., 2004), that incorporates 14 features: articular cartilage integrity, subarticular bone marrow abnormality, subarticular cysts, subarticular bone attrition, marginal osteophytes, medial and lateral meniscal integrity, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, synovitis/effusion, intraarticular loose bodies, and periarticular cysts/bursitis. A BML associated with knee OA may resolve, fluctuate in size, or expand over a short period of time (Zhang et al., 2011b, Garnero et al., 2005). Longitudinal studies have demonstrated that a BML is more likely to progress and grow over time than resolve in patients with knee OA (Hunter et al., 2006, Phan et al., 2006).

Compared to joint space narrowing on traditional radiographs, the presence of BMLs on MRI has been better correlated with the severity of clinical symptoms as well as clinical worsening (Singh et al., 2019). Patients with knee OA and a BML had a nine-fold likelihood of progressing to total knee replacement than controls without a BML (Scher et al., 2008). The presence of a large BML or an increase in BML size has been associated with clinical deterioration and performance of 2.5 - 3.4 times the need for total knee replacement in patients with OA (Roemer et al., 2012). While a complete interpretation of these relationships is lacking, it appears that the presence of a BML is associated with clinical decline, advancement of symptoms and an increased likelihood that a patient will proceed to knee replacement (Singh et al., 2019).

1.4.4 Degenerative Changes of Peri-Articular Structure and Synovium

Recent research supports that OA is a “whole joint” disease (O’Neill and Felson, 2018, Dobson et al., 2018). Although cartilage disintegration is the main feature of the disease, synovitis, subchondral bone remodelling, degeneration of menisci and surrounding ligaments, and hypertrophy of the joint capsule take part in the pathogenesis of OA (Martel-Pelletier et al., 2008). The synovial reaction in OA includes synovial hyperplasia, fibrosis, thickening of synovial capsule, activated synoviocytes, and in some cases, lymphocytic infiltrate (B- and T-cells as well as plasma cells) (Roach et al., 2007). Synovial inflammation plays a vital role in OA's symptoms and structural succession (Ayhan et al., 2014). Inflammatory mediators (cytokines and chemokines) are increased in synovial fluid (SF) in OA and promote synovitis (Loeser et al., 2012). Recent histological studies demonstrated that synovitis might occur even in the early stages of disease, but the prevalence of synovitis increases with the advancing disease stage (Benito et al., 2005, Krasnokutsky et al., 2011). Synovial cells are thought to produce inflammatory mediators, activate chondrocytes, and propagate cartilage breakdown (Berenbaum, 2013). Aiding to this, synovitis has been shown to correlate with severity of symptoms and rate of cartilage degeneration (Scanzello and Goldring, 2012, Ayral et al., 2005, Conaghan et al., 2010, Roemer et al., 2011). Synovitis predicts the development and progression of symptoms (OR 9·2, 95% CI 3·2–26·3) (Scanzello and Goldring, 2012) and possibly cartilage loss (OR 2·7, 95% CI 1·4–5·1) (Roemer et al., 2011), although the relation with structural change is less consistent.

An intact and functional meniscus is essential to preserve joint integrity and avoid any joint damage, but the meniscus plays a much smaller role in symptom genesis (Hunter et al., 2013). Using MRI studies in asymptomatic subjects with a mean age of 65, a tear was found in 67%. Whereas in patients with symptomatic knee OA, a meniscal tear was found in 91% (Bhattacharyya et al., 2003). Meniscal tears are nearly universal in persons with knee OA and are unlikely to cause increased symptoms (Bhattacharyya et al., 2003, Englund et al., 2007).

The role of the muscles around the knee and changes in them should not be overlooked. Periarticular muscles influence joint loading, and any weakness or pain inhibited impairments in muscle function have been observed in people with OA (Hurley, 1999). A longitudinal cohort study investigating factors contributing to poor physical functioning in the patients with knee OA reported that reduced absolute quadriceps and hamstrings strength and poor proprioceptive acuity increased the likelihood of poor physical functioning and increased the chances of progression of OA (Sharma et al., 2003). In addition to this, there is abundant evidence from clinical trials demonstrating that muscle strengthening exercises result in improvements in pain, physical function and quality of life in people with knee OA (Roddy et al., 2005b, Roddy et al., 2005a).

1.5 Inflammation in Knee Osteoarthritis

1.5.1 Inflammatory Process in Osteoarthritis

Inflammation is a protective response controlling tissue damage resulting from pathogenic, traumatic or toxic injury. The inflammatory process is governed by both pro- and anti-inflammatory molecules requiring distinct cell types and various factors that act in a coordinated manner to regulate cell chemotaxis, migration and proliferation, leading to tissue repair (Benelli et al., 2006).

Although, initially considered cartilage driven, OA is a much more complex disease with inflammatory mediators released by cartilage, bone and synovium (Loeser et al., 2012, Kapoor et al., 2010, Goldring and Otero, 2011).

Several other studies supported the observation that systemic inflammation is associated with OA (Sokolove and Lepus, 2013a). These include representing that serum levels of C-reactive protein (CRP) are strongly associated with the presence and evolution of knee OA (Martel-Pelletier et al., 2017). Another study has demonstrated a positive correlation between levels of serum CRP and histologic evidence of synovitis and synovial fluid interleukin-6 (IL-6) (Pearle et al., 2007). These studies suggest that the inflammation observed in OA is at least partially reflective of local synovial inflammation.

1.5.2 Localised Features of Knee Osteoarthritis

Cartilage disintegration is the main feature of the disease. However, synovitis, subchondral bone remodelling, deterioration of ligaments and menisci, and

thickening of the joint capsule take parts in the pathogenesis of OA (Martel-Pelletier et al., 2008).

Besides synovitis, cartilage breakdown products in synovial fluid and micro-fissures in articular cartilage are present before any degeneration can be noted using current MRI technology or arthroscopic visualisation (Pauli et al., 2011, Ayral et al., 2005). The early cartilage degeneration may play a driving role in the development of inflammation in the synovium and within the arthritic joint (Sokolove and Lepus, 2013a).

The joint trauma or overuse can lead to the development of chronic inflammation in OA, which can be described as a vicious, self-sustaining cycle of local tissue damage, inflammation, and repair, a pattern which is seen in a chronic wound (Kragstrup et al., 2019).

1.5.3 Systemic and Metabolic Triggered Inflammation – Metabolic Osteoarthritis

Inflammatory mediators play an essential role in the initiation and progression of OA. The source of such mediators may be local (from joint cells) or systemic (from other tissues) (Ayhan et al., 2014). Recent studies link the local production of inflammatory mediators to a more systemic pathway (Berenbaum, 2013). Levels of several inflammatory mediators are higher in the sera of patients with OA when compared to healthy individuals (Sohn et al., 2012, Fernández-Puente et al., 2011, Attur et al., 2012). One study assessed gene expression profiles in peripheral blood leukocytes (PBLs) from OA

patients and found a subset with activated PBLs (Attur et al., 2012). Interestingly, cluster analysis revealed two distinct subgroups. The first subgroup had an increased level of IL-1β, and the second subgroup had a normal expression. Patients with the inflammatory “IL-1β signature” had higher pain scores and decreased function. Furthermore, they were at higher risk of radiographic progression of OA.

Another peripheral inflammatory marker is adipokine which is released in blood flow and reaches the joint via the subchondral bone vasculature (Berenbaum, 2013, Pottie et al., 2006). Adipokine is associated with adipose tissue found in obese individuals. The risk of hand OA is two-fold in obese patients (Yusuf et al., 2010). This finding explains that obesity as a risk factor for OA is not only linked to the biomechanical model but also to the systemic inflammatory paradigm. Adipokines have been extensively studied in OA. Among them, leptin, adiponectin, resistin, and visfatin/NAMPT have pro- and/or anti-inflammatory properties in OA (Gomez et al., 2011, Gosset et al., 2008, Zeyda et al., 2007). There is an established association between systemic adipokines and local synovial tissue inflammation (de Boer et al., 2012).

Epidemiological and clinical studies have underlined that MetS rather than obesity itself has the most significant impact on the initiation and severity of OA (Gosset et al., 2008, Sowers et al., 2009, Puenpatom and Victor, 2009, Wang et al., 2015, Zhuo et al., 2012). Metabolically triggered inflammation, also known as meta-inflammation (Gregor and Hotamisligil, 2011), can result from abnormalities in body composition, adipokines, cytokines, lipids, and vitamin D and has been associated with the pathogenesis of OA (Wang et al., 2015).

Excessive lipids and glucose could disturb the integration of systemic metabolism leading to inflammatory responses. Additionally, a group of acute phase proteins (complement components), stimulated by pro-inflammatory cytokines, could lead to a chronic inflammatory state and metabolic dysfunction (Wang et al., 2015).

Thus, OA could be initiated and/or aggravated by the presence of low-grade systemic inflammation. Further epidemiological and experimental studies are needed to explore these relationships in-depth (Berenbaum, 2013).

1.6 Pain and Knee Osteoarthritis

1.6.1 Definition of Pain

Pain is defined by the International Association for the Study of Pain (IASP) as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (Raja et al., 2020). A recent article pointed out correctly that pain should not be confused with nociception (Cohen et al., 2018). ‘Nociception’ is defined as a function of a specific sensory system. ‘Nociceptive system’ is a warning system that gets triggered with an adequate stimulus. And, ‘Noxious stimulus’ is a stimulus that is damaging or threatens to damage normal tissues. In comparison, pain is a result of network activity in the brain.

Pain is defined as a subjective experience that debatably occurs only in the person that feels it. This is a first-person perspective, whereas nociception

refers to noticeable activity in the nervous system in response to a stimulus and is a third-person perspective (Treede, 2018).

The new proposed definition of pain is 'Pain is a mutually recognizable somatic experience that reflects a person's apprehension of threat to their bodily or existential integrity' (Cohen et al., 2018). Pain without any apparent tissue damage was well-thought-out "psychogenic" in the 20th century. In this century, we differentiate between nociceptive pain and neuropathic pain. Nociceptive pain is caused by tissue damage, whereas neuropathic pain derives from somatosensory system damage (Boadas-Vaello et al., 2016). A third category has been proposed as 'nociplastic pain' (Kosek et al., 2016). This is primarily intended for patients suffering from chronic pain conditions characterized by evidence of 'altered nociceptive processing'. Fibromyalgia, Irritable bowel Syndrome (IBS) and Complex Regional Pain Syndrome (CRPS) are examples of nociplastic pain without any tissue damage. Whereas, patients suffering initially from nociceptive pain, such as osteoarthritis, may develop alterations in nociceptive processing established as altered descending pain inhibition (Arendt-Nielsen et al., 2010, Kosek and Ordeberg, 2000a) accompanied by spread of hypersensitivity (Kosek and Ordeberg, 2000b, Aranda-Villalobos et al., 2013, Graven-Nielsen et al., 2012).

1.6.2 Knee Osteoarthritis and Pain Generation

The predominant symptom in most patients presenting with OA is pain (Hunter et al., 2008b). The determinants of pain in OA are not well understood but are believed to involve multiple interactive pathways that are best framed in a

biopsychosocial framework (Hunter et al., 2013). This framework pays attention to biological, psychological and social factors, and these play a significant role in OA related pain generation (Dieppe and Lohmander, 2005, Hunter et al., 2008a). Psychosocial factors that can influence symptoms include self-efficacy and pain catastrophizing. The social context of arthritis (social support, understanding of pain, pain communication) is essential in understanding the pain experience (Hunter et al., 2013).

Neuronal activity in nociceptive pathways generates signals that ultimately are interpreted as ‘joint pain’, ‘somatic pain’ or ‘nociceptive pain’. The biological contribution to pain stems from the multitude of tissues within the joint containing nociceptive fibres, which are the sources of pain in OA. The subchondral bone, periosteum, joint capsule with its synovial lining, peri-articular ligaments and periarticular muscle are all innervated and likely sources of nociception in OA (Hunter et al., 2013). However, individuals with the same degree of structural damage experience different pain levels, a phenomenon that is poorly understood (Hunter et al., 2008a). While this is not fully understood, some of this may be due to ‘central sensitisation’. During acute or chronic inflammation or soft tissue injury, chemical mediators are released into the joint that sensitize primary afferent nerves in a way that normally harmless joint movements (such as walking with pace or increase physical activity) may produce a painful response (Hunter et al., 2013). Over time, this increases neuronal activity from the peripheral region creates peripheral sensitisation, which ultimately can contribute to plasticity changes in the central nervous system termed as ‘central sensitisation’ (Woolf and Salter, 2000). A study involving quantitative sensory testing (QST) (Finan et al.,

2013a) reported that patients with mild to moderate OA reported on radiographs but presenting with severe levels of pain were the most pain-sensitive patients. This discrepancy between pain perception and radiographic features of knee OA may be explained by the vulnerability of some patients to develop central sensitisation to pain, a pain-magnifying neuroplastic change considered to be a risk factor for developing chronic pain (Nijs et al., 2011).

The damage to the nervous system centrally or peripherally can lead to 'neuropathic pain' (Cohen and Mao, 2014). Neuropathic pain can develop after nerve injury (to the joints, muscles or capsule) when harmful changes occur in injured neurons and along nociceptive and descending modulatory pathways in the central nervous system. Neuropathic pain can be differentiated from non-neuropathic pain by two factors. Firstly, in neuropathic pain, there is no transduction (conversion of a nociceptive stimulus into an electrical impulse). Secondly, the prognosis is worse: injury to major nerves or central nervous system is more likely the case than injury to the joint capsule, bone and tendons (non-nervous tissues), resulting in chronic pain (Cohen and Mao, 2014). In addition, neuropathic pain tends to be more recalcitrant than non-neuropathic pain to conventional analgesics (NSAIDs and opioids). However, because of the substantial overlap between neuropathic and nociceptive pain in terms of processes and treatment modalities, it might be difficult for the clinicians and patients to differentiate how much of these contribute individually to patients' overall pain.

In individuals with central sensitisation, second-order neurons in the spinal cord become more reactive to peripheral signals and start responding to lower-threshold stimuli that would not usually cause the neurons to fire. In this

instance, nociceptive information to the somatosensory cortex is enhanced. Central sensitisation can exaggerate the sensation of pain and even lead to pain responses from regions of the body distant from the site of initial injury or arthritic inflamed joint (Hunter et al., 2013). This is termed as ‘referred pain’. This type of “referred pain” is not a nociceptive process; it is neuropathic in origin, even if momentary.

There is ‘widespread’ / ‘other’ pain that may not fit into somatic, referred or neurogenic pain. Pain in Fibromyalgia is one example, and historically, these widespread pains have often been called ‘functional pain disorders’ (Schechter, 2014). This has already been covered under the previous sub-heading 1.6.1 as ‘nociplastic pain’ (last paragraph).

1.6.3 Radiographic OA and correlation with pain

Pain is a vague symptom of knee OA, and its association with radiographic anomalies varies according to the extent of radiographic changes and radiographic view (Heidari et al., 2016). Various studies have investigated the relationship between pain and radiographic changes in individuals with knee OA reaching different conclusions. This may be attributed to types, severity, and the prevalence of radiographic anomalies (Schiphof et al., 2013, Bedson and Croft, 2008) studied. The clinical and radiographic features of knee OA are not usually agreeable with knee OA symptoms (Heidari et al., 2016).

A systematic review reported that only 15-76 % of subjects with knee pain had radiographic features of knee OA, and only 15-81% of subjects with radiographic OA had knee pain (Bedson and Croft, 2008). They reported that

the association between radiographic changes and pain varied from none to strong. However, the presence of severe radiographic changes was strongly associated with pain.

In contrast to the above, the Baltimore Longitudinal Study of Aging studying participants over a 5-year follow-up period reported that all measures of radiographic severity were directly correlated with knee pain (Lethbridge-Cejku et al., 1995). Another study involving two cohorts of the United States population (overall n= 1032) has demonstrated a strong association between pain (assessed by using WOMAC – Western Ontario and McMaster Universities Index) and x-ray findings (Neogi et al., 2009). They reported a strong dose-response relation between severity of radiographic knee osteoarthritis and knee pain, as measured by three attributes: the presence of frequent knee pain, consistency of knee pain, and severity of knee pain. They compared both knees in their participants, thus eliminating between-person confounding, allowing them to obtain valid effect estimates of radiographic osteoarthritis on knee pain.

A recent cross-sectional study enrolled 25 patients with knee OA with the clinical and radiographic diagnosis of bilateral OA (Kellgren-Lawrence grading scale 1- 4 on x-ray images), but pain symptoms in only one knee (Vargas E Silva et al., 2020). They collected demographic data, self-reported pain (VAS-visual analogue scale), superficial knee temperature and pressure pain thresholds (PPT). They have reported discordance between pain perception (VAS) and Kellgren-Lawrence (K/L) classification; however, significant weak and moderate associations were found between radiographic classification (K/L) of OA and PPT of both knees in almost all sites evaluated (except vastus

lateralis muscle). This study has some limitations and, most remarkably small sample size. This might be a potential reason not to see a correlation between pain reported on VAS and different classifications of knee radiographs. Additionally, the study's cross-sectional nature prevents further cause-effect conclusions for the weak association found between PPT and knee radiographs.

Several reasons may account for these apparently contradictory results regarding the link between the severity of pain and the severity of radiographic osteoarthritis. These include but are not limited to selection criteria for the patient population, i.e., individuals with knee OA as the test group or individuals with chronic knee pain on which the presence of radiographic OA was then tested, using different knee radiograph protocols and different criteria for scoring x-rays. A systematic review studying the association between radiographic and clinical osteoarthritis of hip and knee OA hypothesized that the discrepancy in the detection of an association might be caused by different definitions of OA, by different radiographic protocols, and by scoring methods for radiographic damage and symptoms in various studies (Kinds et al., 2011). Their literature search resulted in 39 studies describing an association between the radiographic and clinical knee and hip OA. They reported that the frequency of an association between radiographic and clinical OA outcome measures diminished when fewer quality criteria were fulfilled. Additionally, only four studies were identified that fulfilled all quality criteria, and, in these studies, an association was found for the knee joint pain and radiographic scoring (K/L). They concluded that methodological quality criteria are of significance to reveal an association between radiographic and clinical OA.

Another reason for discordance between pain perception of knee OA sufferers and K/L scoring may be due to the presence of central sensitisation. A study involving quantitative sensory testing (QST) (Finan et al., 2013a) observed that patients with severe levels of clinical pain and no evidence of moderate to severe radiographic evidence of knee OA were the most pain-sensitive. This discrepancy between pain perception and radiographic features of knee OA may be described by the vulnerability of some patients to develop central sensitisation to pain, a pain-amplifying neuroplastic change considered to be a risk factor for developing chronic pain (Nijs et al., 2011).

Personal experience of the author is that if certain factors (x-ray views, same clinician assessing radiographs and clinical assessment, similar ethnicity of patients) are kept controlled in a clinical setup, then there is an association between the pain reported by patients and severity of knee OA observed on radiographs, especially when radiographs are showing severe knee OA and pain reported by the patient is ‘significant’ as reported by earlier mentioned systematic review (Bedson and Croft, 2008). The discordance is not as strong as once thought, especially when study designs are improved and flaws are minimised as reported by earlier studies (Neogi et al., 2009, Duncan et al., 2007, Kinds et al., 2011). However, the discordance can be observed in a clinical setup when radiographs show only mild-moderate knee OA, but patients report significant knee pain, and this is likely to be caused by the presence of central sensitisation once soft tissue derangement such as meniscal, cruciate, and collateral ligaments are ruled out during clinical assessment or using diagnostics such as MRI scan. To summarise, radiographic features usually do not fully correlate with knee OA sufferers

reported pain; however, there is some degree of concordance between radiographic features and reported pain.

1.7 Sleeping Disturbances and Prevalence of Osteoarthritis

Sleep is normally described as a recurring state of reduced or lack of consciousness, inactivity of voluntary muscles, decreased ability to react to stimuli (compared to quiet wakefulness), but is more easily reversible than coma, vegetative state or deep sedation (Goupil and Bekinschtein, 2012). Sleep is seen as a submissive state that develops in the absence of wakefulness.

OA creates potentially debilitating physical and psychological problems, making individuals particularly vulnerable to comorbid disorders that may exacerbate OA-associated symptoms (Parmelee et al., 2015a). Sleep disturbance is one such comorbidity. Studies including participants suffering with knee OA reported up to 31% significant disturbances initiating sleep, 81% having difficulties maintaining night-time sleep, and up to 77% having any sleep problem (Pickering et al., 2016, Park et al., 2019).

The relationship between sleep and pain is established and bidirectional (Wilcox et al., 2000, Smith et al., 2009a, Dzierzewski et al., 2010, Parmelee et al., 2015a, Salazar et al., 2014, Stocks et al., 2018). Spielman's model of chronic insomnia explains that pain may serve as a triggering factor that interacts with certain predisposing features (e.g., tendency toward

physiological hyperarousal) to initiate and maintain sleep disturbances (Spielman et al., 1987). Sleep problems (e.g., difficulty initiating sleep, sleep fragmentation) may disturb various physiological processes that affect pain perception. Sleep deprivation may lead to increased C-reactive protein and interleukin-6 levels (Patel et al., 2009, Fine, 2015) and one-third reduction in glucose metabolism (Spiegel et al., 1999). These changes at cellular levels and within the body lead to a pro-inflammatory environment, ultimately leading to local hyperalgesia and widespread pain (Zhang and An, 2007, Feinberg et al., 2017, Sproston and Ashworth, 2018, Zhou et al., 2016, Zhai et al., 2016). In a clinical context, an example would be a patient presenting with sleep deprivation leading to localised allodynia of knee joint and generalised pains because of these cytokines and metabolic issues, though clinically, it is impossible to imply that allodynia and generalised aches are pure results of sleeping disorders. It is not only ascending sensory pathways leading to pain provocation as a result of sleep deprivation, but further studies suggest that the hyperalgesic effect of sleep deprivation is mediated by impairments in the descending pain modulatory systems (Tiede et al., 2010, Finan et al., 2013b, Stocks et al., 2018). A small with-in person (n=10) study instructed to restrict themselves to four hours or less of sleep in their home environment for one night, and sleep duration was verified with actigraphy (Tiede et al., 2010). The next day, they assessed their participants using quantitative sensory testing (QST). The results of QST for these participants after partial deprived sleep were compared with the results of QST from another day after having a habitual sleep. Noxious stimuli were rated as significantly more painful following partial sleep deprivation compared to uninterrupted sleep. They suggested that the

augmented pain was due to partial sleep deprivation and was facilitated by impairments in the descending pain modulatory systems rather than an augmentation of the ascending sensory pathways. However, due to the small sample size, further research is required to confirm this. Increased pain perception following experimental interruption of sleep may be particularly relevant to patients with chronic pain, as they have been shown to functionally alter key endogenous pain modulatory pathways known to increase vulnerability to central sensitization and persistent pain (Smith et al., 2007, Finan et al., 2013b).

A similar relationship is proposed by Smith and colleagues, whereby disrupted sleep may contribute directly to increased central pain perception, thus exacerbating daily pain, which may then disseminate sleep disturbances (Smith et al., 2009a). A possible explanation for this finding is that sleep disturbance may engage multiple pain modulatory pathways within the central nervous system through inflammatory mediators or N-methyl-d-aspartate receptor activation (Smith et al., 2009a, DelVentura et al., 2014). Consequently, activation of these mechanisms is linked with reductions in pain thresholds, pain inhibition, and enhanced temporal summation of pain (i.e., enhanced pain in response to repeated noxious stimuli) (Petrov et al., 2015).

The relationship between sleep disturbances and the severity of pain in knee OA is usually explored. Sleep disturbances such as shortened sleep duration and fragmented sleep (Wilcox et al., 2000) have been associated with increased sensitivity to knee OA pain and, consequently, decreased quality of life (Smith et al., 2009a) in the sufferers of knee OA. Disturbed sleep is a frequent complaint of people experiencing chronic pain, such as those with

knee OA (Parmelee et al., 2015b, Parmelee et al., 2015a, Power et al., 2005, Smith et al., 2009b, Stebbings et al., 2010, Hawker et al., 2010, Hopman-Rock et al., 1996). The resultant changes in sleep architecture can affect health even in the presence of apparently adequate sleep duration. For example, an insufficient amount of slow-wave sleep associates with hypertension, type 2 diabetes mellitus, poor cognition and obesity (Fung et al., 2011, Levendowski et al., 2012, Mesarwi et al., 2013, Ancoli-Israel and Cooke, 2005, Cricco et al., 2001, Ancoli-Israel, 2009). Sleep disturbances are present in 67–88% of people with chronic pain, and ≥50% of individuals with insomnia have chronic pain (Senba, 2015, Levendowski et al., 2012). Therefore, studying the sleeping pattern is highly relevant if we discuss a successful online exercise programme for knee OA.

1.8 Management of Osteoarthritis

1.8.1 Recommendations for managing Knee Osteoarthritis Globally

Currently, there is no cure for OA (Fransen et al., 2015, Huang et al., 2018, Raposo et al., 2021); however, the focus of treatment should be on symptomatology relief from OA (Tanaka et al., 2014). Many national and regional guidelines have been developed to assist clinicians and Healthcare Professionals (HCPs) in managing knee OA (Hochberg et al., 2012, Jordan et al., 2003, Vogels et al., 2001, Zhang et al., 2007, Members et al., 2001, Zhang et al., 2008).

Osteoarthritis Research Society International (OARSI) has published multiple guidelines for knee, hip and polyarticular OA (Zhang et al., 2007, Zhang et al., 2008, Zhang et al., 2010, Bannuru et al., 2019, McAlindon et al., 2014). OARSI aims to present a universally agreed core set of recommendations for the management of knee OA and is usually recommended worldwide. To achieve optimal management of individuals with knee OA, OARSI guidelines recommend offering a person-centred approach using a combination of pharmacological and non-pharmacological strategies. This principle is also supported by the European League Against Rheumatism (EULAR) (Fernandes et al., 2013), the American College of Rheumatology (ACR) guidelines (Hochberg et al., 2012) and the National Institute for Health and Care Excellence (NICE, 2020).

The most recent non-surgical guidelines presented by OARSI are shown in Figure 1-2. These cover knee OA with and without co-morbidities and also consider multiple joint OA. With regard to non-pharmaceutical treatments, their recommendations are provision of exercise programs (land-based, water-based, and strength training) for individuals with knee OA as well as weight loss programs for overweight individuals with knee OA. They recommended against transcutaneous electrical nerve stimulation (TENS) and were uncertain about Electromyogram (EMG) biofeedback. They were unsure of the role of acupuncture in the management of knee OA. They recommended the use of biomechanical interventions (medially wedged insole).

These guidelines documented “Inconclusive” recommendations for acetaminophen, hyaluronic acid treatment, and intra-articular corticosteroids with regard to pharmaceutical treatment strategies. They recommended

against chondroitin and glucosamine. Topical NSAIDs are strongly recommended, but oral NSAIDs (both non-selective and COX-2 selective) have a conditional recommendation to use on those who do not have comorbid conditions. They provided an “Uncertain” recommendation for duloxetine in individuals with knee-only OA and co-morbidities. The use of intra-articular corticosteroids was conditionally recommended in individuals with knee OA in all comorbidity groups, noting that steroid injections given to knee joints may provide short-term relief.

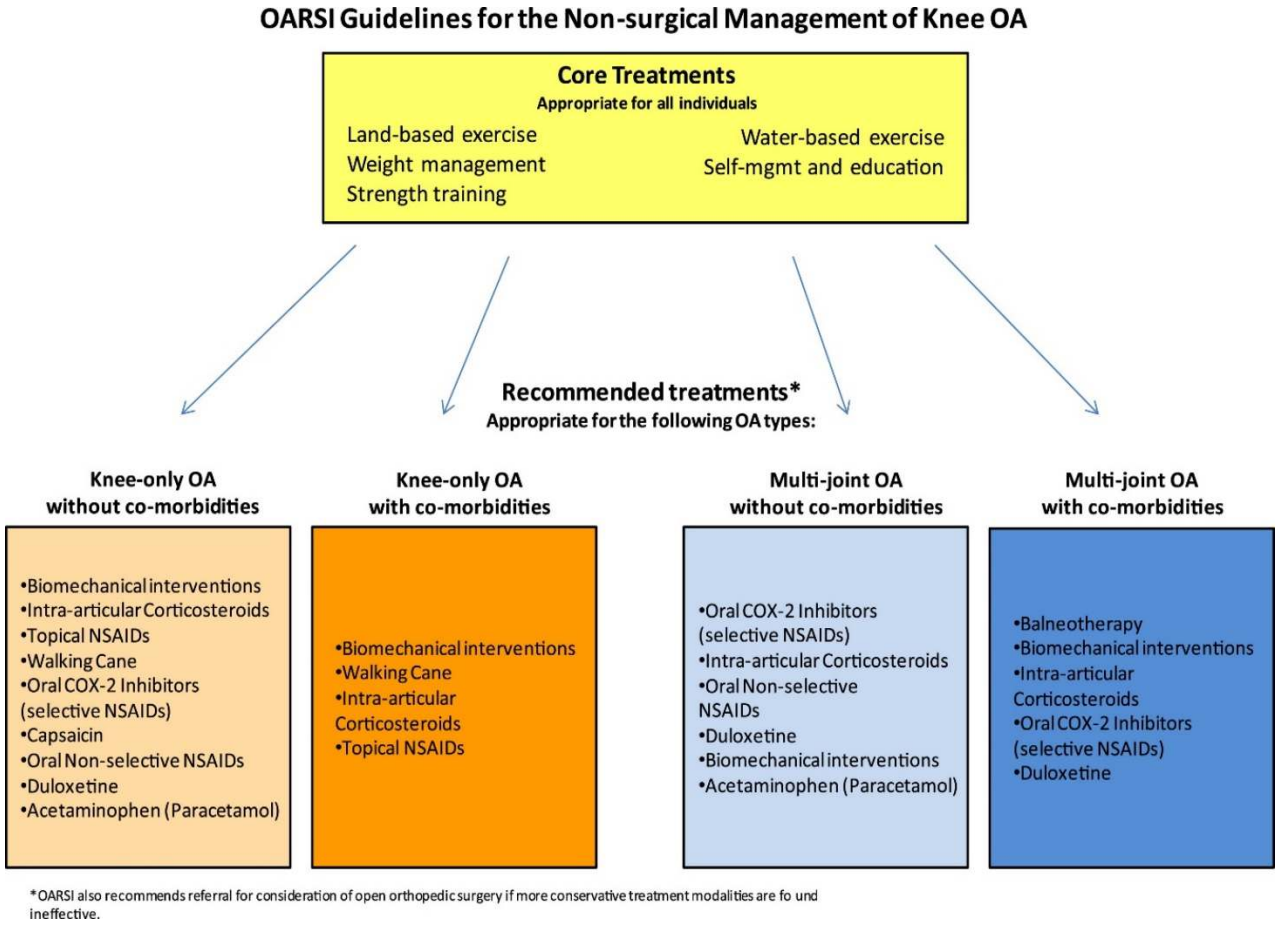


Figure 1-2: OARSI guidelines for non-surgical management of Knee OA (McAlindon et al., 2014)

These guidelines were developed by rheumatologists, orthopaedic surgeons, physical therapists, a primary care physician, a physiatrist, and a clinical

epidemiologist. These guidelines excluded cost-effective analysis and evaluated treatments solely based on their safety and efficacy profiles. This is one of the limitations of these guidelines. These guidelines focused primarily on the non-surgical management of knee OA, though they recommended referral for consideration of orthopaedic surgical interventions after conservative treatment options have been exhausted.

1.8.2 Management of Knee OA in the United Kingdom

In the United Kingdom, the National Health Services (NHS) provide treatment for different medical conditions. As it is publicly funded, therefore it must be cost-effective. Cost-effectiveness is the key element and is given high importance while developing any guidelines. These guidelines are usually developed by the National Institute for Health and Care Excellence (NICE).

The NICE guidelines for OA (NICE, 2020) have recommended three mains divisions of the treatment. These are core treatment options, adjunct non-pharmacological and adjunct pharmacological treatments for OA shown in Figure 1-3. Starting at the centre and working outwards, the treatments are arranged in the order they should be considered, considering individuals' different needs, risk factors, and preferences. The core treatments (centre) should be considered first for every person with osteoarthritis. If further treatment is required, consider the drugs in the second circle before the medications in the outer ring are trialled. The outer circle also shows adjunctive treatments (both non-pharmacological and surgical), which have less well

proved efficacy, provide less symptom relief, or have increased risk to the patient than those in the second circle.

The core treatment consists of providing advice on the following:

- Access to appropriate information, oral and written, enhances understanding of the condition and counters misconceptions.
- Activity and exercise, including local muscle strengthening and general aerobic fitness.
- Interventions to achieve weight loss if the person is overweight or obese.

The adjunct non-pharmacological components include self-management strategies, positive behavioural changes, local heat or cold applications, suitable footwear for pain and stability (insoles), transcutaneous electrical nerve stimulation (TENS), and assistive devices (walking aids or sticks).

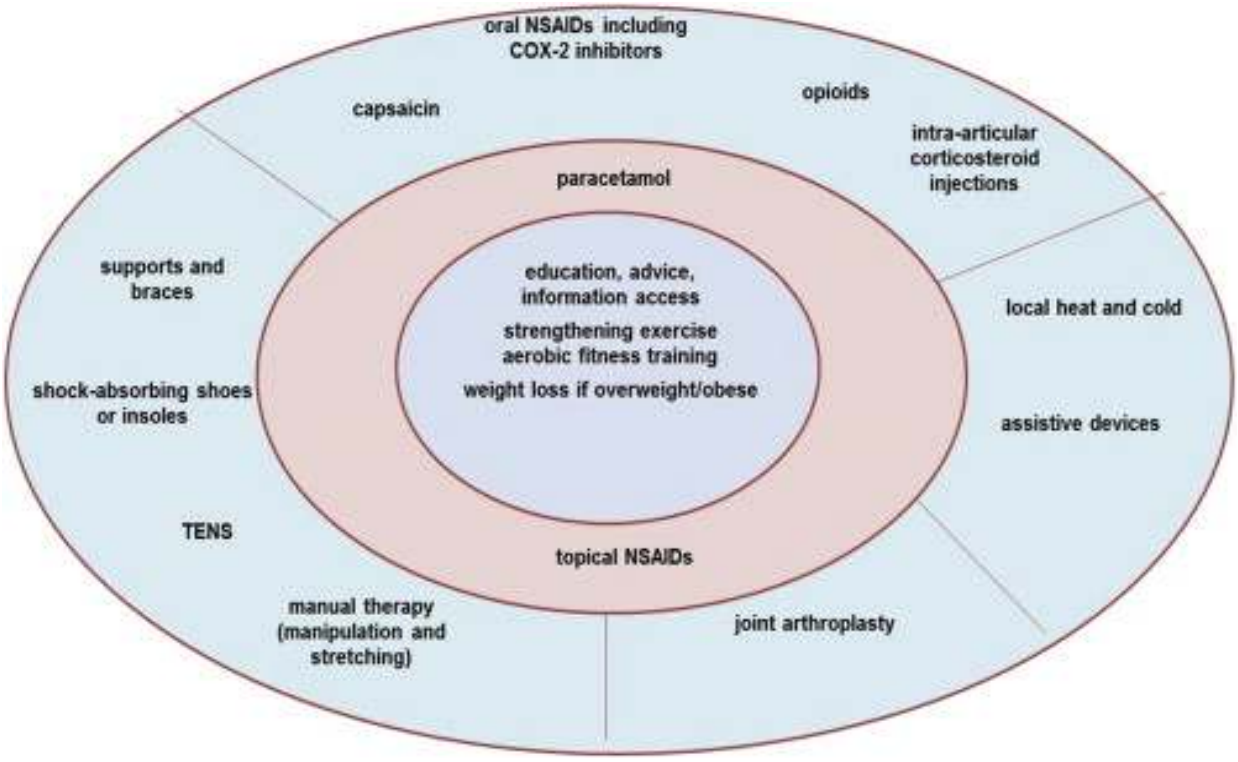


Fig 1-3: Treatments for osteoarthritis in adults. (Ong et al., 2014)

Finally, the adjunct pharmacological treatments include prescribing to manage arthritis. The recommendations are to consider the risk and benefits of pharmacological treatments, particularly in older people and those with comorbidities. The suggestions are to try:

- Paracetamol and topical non-steroidal anti-inflammatory drugs (NSAIDs). This should be offered before oral NSAIDs and cyclo-oxygenase-2 (COX-2) inhibitors or opioids are trialled.
- Opioid analgesics if paracetamol and topical NSAIDs are inefficient for pain relief or replace them with oral NSAIDs or COX-2 inhibitors at the lowest effective dose for the shortest period of time.
- Intra-articular steroid injections when pain is moderate to severe.

When these measures fail, then patients should be referred for surgical options. The NICE guidelines suggest:

- Before referring patients for joint surgery, ensure that they have been offered at least core treatment options.
- Consider referral for joint replacement surgery for those patients who have joint symptoms (pain, stiffness, and reduced function) that substantially affect their quality of life and are refractory to non-surgical treatment. Referral should be made before prolonged and established functional limitation and severe pain.
- Patient-specific factors (including age, sex, smoking, obesity, and comorbidities) should not be barriers to referral for joint replacement surgery.

- Onward referral decisions should be based on discussions between patient representatives, referring clinicians, and surgeons rather than current scoring tools for prioritisation.

Despite national and international treatment guidelines, evidence suggests a gap between the recommendations and what patients receive in the UK (Porcheret et al., 2007). No study looked at the gap between the recommendations and actual implementation. The Management of Osteoarthritis In Consultations (MOSAICS) study is the first study to determine the effectiveness of a model OA consultation (MOAC) based on the recommendations of NICE guidelines (Dziedzic et al., 2014, Dziedzic et al., 2018). There were four GP practices in the intervention and control arm each. Control practices received no training, guidebook or dedicated nurse in OA clinic and continued usual care. The intervention in MOSAICS was an initial GP consultation with up to 4 follow up visits with practice nurses. Only 29% of patients in the intervention arm reported having a consultation with nurses. No difference was found between the intervention and control group practices on the primary clinical outcome (physical functioning) at six months. The exception is the reduction in x-ray requests and oral NSAIDs, whereas an increase in paracetamol prescription in the intervention groups was observed over six months.

1.9 Exercises Intervention for Osteoarthritis

Current clinical guidelines for the non-surgical management of knee OA recommend exercise, information and, in relevant cases, weight loss

(Conaghan et al., 2008, Jevsevar, 2013, Pendleton et al., 2000, Bennell et al., 2012, Hochberg et al., 2012, Fernandes et al., 2013, McAlindon et al., 2014). There is reasonable evidence for the effectiveness of exercise intervention in the management of knee OA and to improve the functional capacity of these individuals to cope better with the activities of daily living (Bennell and Hinman, 2011, Messier et al., 2004, Thomas et al., 2002, van Baar et al., 1999, Chamberlain et al., 1982, Ettinger et al., 1997b, Ettinger et al., 1997a, Kovar et al., 1992, Minor et al., 1989, Fisher et al., 1991, Pisters et al., 2007, Hurley et al., 2007, Dunlop et al., 2011, Esser and Bailey, 2011, Lange et al., 2008, Bartholdy et al., 2018, Zhang et al., 2008, Juhl et al., 2014, Fransen et al., 2015, Bartholdy et al., 2017). In fact, one study reported a slow-down of progressive radiographic changes of knee OA as a result of knee strengthening exercises (Mikesky et al., 2006). Despite this evidence, it is still unclear which programme or type of exercise is more effective when treating knee OA (Dong et al., 2018). There is a significant disparity in the opinions regarding the effectiveness of different types of exercise to manage pain in knee OA patients, and a combination of open and closed chain isotonic exercises are recommended for knee OA (Baker and McAlindon, 2000).

A recent systematic review concluded that pilates, aerobics and strengthening exercise programmes performed for 8-12 weeks, 3-5 sessions per week, and each session lasting 1 hour appears to be an effective treatment for knee OA, mainly regarding knee pain and strength improvements (Raposo et al., 2021). They screened 3222 articles, and only 19 articles met the eligibility criteria. The most common types of exercise were strengthening and aerobics. The most common outcome was pain, and 15 out of 19 studies measured pain. This

systematic review reported that ten randomised controlled trials out of 15 studies that measured pain found a significant improvement in pain (effect size [ES] between 0.06 and 1.2). Out of various exercises improving pain, stationary cycling was the type of exercise that showed the highest effect size (ES = 1.2), with a frequency of 5 days a week, for 12 weeks, each session lasting 1 hour. They also reported benefits on strength, however evidence favouring improvement on function, quality of life and functional performance was reported controversial by studies included in this systematic review. There are few limitations of this systematic review. Firstly, some studies included in this review did not report effect size and data were not presented; therefore, authors could not calculate the effect size for those studies. Additionally, some studies that reported significant improvements demonstrated low effect size, limiting the capacity to generalise this information to clinical practice. Lastly, they could not conduct a meta-analysis due to distinct outcomes and assessment tools for these outcomes.

One of the fundamental issues is that most RCTs compare exercise interventions to control groups having no intervention. Therefore, direct comparison between different interventions in RCT study is impractical or very costly to most research teams. This is where network meta-analysis is valuable and try to fill in those gaps where RCTs comparing different exercise interventions are far and few (Caldwell, 2014). Network meta-analysis by Uthman et al. (2014) examined twelve exercise interventions plus no exercise control for lower limbs (aerobic, flexibility, strengthening, flexibility+strengthening, flexibility+aerboics, strengthening+aerobics, strengthening+flexibility+aerobics, aquatic strengthening, aquatic

flexibility+strenthening, aquatic flexibility+aerobic, aquatic strenthening+aerobic, aquatic aerobic+flexibility+strengthening) and examined pain and function as outcomes. The overall difference in pain intensity versus control was −2.03 cm (95% CI −2.82 to −1.26 cm, large effect size) on the visual analogue scale for strengthening only exercise, −1.74 cm (95% CI −2.60 to −0.88 cm, medium effect size) for flexibility plus strengthening plus aerobic, −1.26 cm (95% CI −2.12 to −0.40 cm, medium effect size) for flexibility plus strengthening exercise, −1.87 cm (95% CI −3.56 to −0.17, medium effect size) for aquatic strengthening, and −1.87 cm (95% CI −4.11 to −0.68 cm, large effect size) for aquatic flexibility plus strengthening exercise. In terms of the cumulative probability of being the overall best exercise intervention for pain in lower limb osteoarthritis, aquatic strengthening plus aerobic flexibility exercise (81%) was closely followed by strengthening exercise only (76%), and aquatic strengthening plus aerobic exercise (73%). The combined intervention of strengthening plus flexibility plus aerobic exercise was significantly more effective than no exercise controls for function. The overall difference in function versus no control was −1.32 units (95% CI −2.44 to −0.21 units, medium effect size) on a WOMAC disability scale ranging from 0 to 10 for the combination of strengthening, flexibility, and aerobic exercise. This combination of strengthening, flexibility, and aerobic exercise (71%) and aquatic strengthening plus aerobic (71%) exercises had the highest probability of being the best overall treatment for function (Uthman et al., 2014).

A recent systematic review and network analysis reviewed 103 trials (n=9134) (Goh et al., 2019b). In addition to strengthening, aerobic and flexibility exercises, they included mind-body exercise and a ‘mixed’ exercise category.

Mind-body exercises are integrated mindfulness/relaxation strategies into physical movements/exercises such as tai chi or yoga. The mixed exercises category can be a combination of any of these exercises. Their primary outcome was pain, and secondary outcomes were self-reported function, objective performance (e.g. walking speed, range of motion, strength), and quality of life. They reported that aerobic exercises were most beneficial for pain (ES 1.11; 95% CI: 0.69-1.54) and performance (ES 1.05; 95% CI: 0.63-1.48). Mind-body exercises were found to be equally effective for pain (ES 1.11; 95% CI: 0.63, 1.59) and were best for function (ES 0.81; 95% CI: 0.27, 1.36). Comparing these exercises to strengthening exercises, strengthening and flexibility exercises had a moderate ES for pain, function and performance, whereas mixed exercise yielded the minimum ES for all outcomes. One of the limitations of this meta-analysis is the inclusion of studies assessing short term intervention (8 weeks) and treatment exercise for a single joint. Additionally, they had to rely on the authors' description of exercises and control groups in included studies. Also, exercise programmes and ‘usual care’ were not standardised in different studies and varied. This study and previously mentioned studies emphasized that exercise helps reduce pain and recommended the type of exercises to be performed.

The general pain relief following exercise therapy could be due to the pain gate control mechanism (peripheral synaptic decrease in pain fibre action potential due to motor neuron activity) (Wall, 1978, Ropero Peláez and Taniguchi, 2016, Hodges and Tucker, 2011) usually seen with strengthening exercises (Juhl et al., 2014). However, for aerobics, the mechanism is driven by the central release of endorphins (Schwarz and Kindermann, 1992, Brosseau et al., 2017,

Scheef et al., 2012). In healthy participants, aerobic exercises with an intensity of 70 % VO2 max, considered as vigorous aerobic exercise, produced pain inhibition for up to 30 minutes post-exercise (Koltyn, 2002). This hypoalgesia is also observed immediately after a 25-minute vigorous aerobic exercise of stationary cycling at 70% heart rate as well as after a moderate aerobic exercise consisting of stationary cycling at 50% heart rate amongst healthy volunteers (Naugle et al., 2014). The results of a recent systematic review of trials on high-intensity versus low-intensity exercise for knee osteoarthritis revealed that there was inadequate evidence to determine whether different intensity levels of exercise programs predisposed the clinical benefits of reduced pain (Regnaux et al., 2015). Contrary to this, for strengthening exercises, Juhl et al. (2014) reported that a minimum of three times a week exercising and at least 12 supervised sessions seemed to be important and effective for pain relief.

There is an additional clinical question. What if knee OA patients cannot do aerobics or isokinetic or isotonic open/close chain exercises, as one may encounter such patients in a clinical setup? Isometric exercises might be an answer. They are simple to perform and rapidly improve muscle strength (Huang et al., 2018). Individuals who find open and closed isotonic exercises difficult and painful should trial isometric exercises of the knee extensor muscles (Baker and McAlindon, 2000). This study has made this suggestion because some patients cannot do isokinetic or isotonic exercise due to the severity of knee pain. On further search, the author (SG) struggled to find studies on an isometric strengthening exercise programme as a standalone intervention and its effects on knee pain in knee OA sufferers. Most exercise

interventions used in scientific studies were usually a combination of isotonic and isometric exercises or a combination of isometric, aerobics and/or proprioception exercises. This would make it difficult to establish the benefit of isometric exercises as a solo intervention. A recent RCT compared the intervention group (n=128) trialling isometric quadriceps exercise versus the control group (n=122) trialling local physiotherapy and NSAIDs for 1 and 3 months (Huang et al., 2018). They trialled two sets of 10 repetitions of three isometric exercises (in supine, lateral and sitting position) performed in the morning and evenings (twice/day) in knee OA patients. The control group received routine physiotherapy and NSAIDs, and the research team could not standardise physiotherapy intervention in this group. They used the visual analogue scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire as outcome measures. They reported that the VAS score was reduced from 55.1 (baseline score) to 41.0 (at one month) after treatment in the intervention group ($P < 0.05$) and was further reduced from 55.1 (baseline) to 32.0 (at three months) ($P < 0.05$), but there was no apparent statistically significant difference ($P > 0.05$) in the control group between 1 (reduced from baselined score 52.3 to 49.2) and three months (reduced from baseline score 52.3 to 42.2) after treatment. The WOMAC results showed minimal improvement in joint function in the intervention group at one month after treatment (reduced from 33.8 on WOMAC to 29.7; $P > 0.05$), but significant improvement at three months (reduced from 33.8 on WOMAC to 18.7; $P < 0.05$); the control group was improved at one month after treatment (reduced from 34.9 on WOMAC to 28.2; $P < 0.05$), but no further improvement was noted at three months (reduced from 34.9 on WOMAC to 27.1; $P > 0.05$).

The limitation of this study is that they could not standardise the physiotherapy intervention given to the control group, and seven participants in the intervention group required celecoxib (oral NSAID), though used less than three times during the study period. This usage of oral NSAID might have affected the results of this study.

In an attempt to manage knee OA, symptoms of knee arthritis can be exacerbated by following ineffective or unsafe exercise regimens, leading to poor prognosis and poor adherence to exercises intervention (Peeler and Ripat, 2018). Hence the need to choose the type and frequency of exercise intervention carefully.

1.10 Concept of Digital Health in the prevention of Osteoarthritis

The use of social media is a bottom-up, consumer-driven phenomenon that is changing the demand for and access to health information (Gagnon and Sabus, 2015). Many individuals look for health care information online, with many searching online sources for self-diagnosis or diagnosing someone else or improving their knowledge on specific conditions or diseases (Gagnon and Sabus, 2015, Fox S, 2013). People living with chronic illnesses are predominantly likely to pursue peer-to-peer social media sites for support (Fox, 2011). Social media and technology can affect health behaviours and decision making and have become part of the public health landscape (Chou et al., 2009, McNab, 2009, Salathé and Khandelwal, 2011, Centola, 2013). The

Internet delivers an increasingly valuable source for clients' health services, from online coaching for weight loss, muscle strengthening, and smoking cessation to web-based appointment scheduling (Hawn, 2009). Although most of these efforts focus on organisational instruments for providing clients with improved customer services, an equally important use of social media has come from the development of peer-driven health communities (Centola, 2013). Peer-to-peer support in the health sector has a long history, starting with the creation of interaction groups for weight control, alcohol and tobacco abstention, long-term treatment for chronic conditions, and trauma counselling (Kiesler, 1985). Participants' personal and empathetic interaction in these peer groups adds value to these counselling groups (Kaplan et al., 1977, Centola, 2013). The reasoning of this kind of interaction has been expanded into the virtual realm with the development of online tools for education and abstention, and the idea of social support from online interactions has been around since the establishment of the Internet world (White and Dorman, 2001). For example, American Centre of Research (ACOR) provides an open network for patients and their families to share treatment experiences and to participate with a compassionate community (Fogel et al., 2002). The remarkable evolution of Internet-based health and wellness societies allows patients from a variety of social and geographic backgrounds to share and learn information about novel health resources, ranging from information about diet and nutrition to opportunities to learn about patient encouragement, preventive health screenings, and new treatment interventions (Wheeler, 2007, Centola, 2013). Interacting online in different peer groups can change their behaviour to seek

further guidance to improve and sustain healthy lifestyle, thus changing their health behaviours (Centola, 2013).

In addition to facilitating social interactions, online social media increasingly offers an accurate record of health behaviours. Contacting GPs, joining a gym, and shopping for health and beauty products become increasingly routine online activities, and these digital signs of everyday life provide direct reflections of the health-related behaviours that people engage in (Hicks et al., 2019, Najm et al., 2019). Moreover, as these activities lead to new intentionally designed online health communities and applications (apps), large numbers of people maintain their records of workout and diet behaviour in the online forms, providing an accurate description of daily health behaviour as there has ever been (Najm et al., 2019, Centola, 2013). Health care providers have acknowledged and responded to the fact that individuals rely on Internet sources and social media for health information and in making their health care decisions. Therefore, social media usage among health care providers has risen over the past several years (Von Muhlen and Ohno-Machado, 2012).

Because of the high prevalence of knee arthritis, strategies to deliver exercise interventions that are efficacious and cost-effective become a priority. In light of the increasingly digitalised healthcare (Kostkova, 2015), developing web-based exercises can be useful to manage knee OA as online exercises have proven to be useful in other health conditions, including cancer patients (Ariza-Garcia et al., 2019, Galiano-Castillo et al., 2016), obese patients (Ballin et al., 2020), patient with neurological conditions such as multiple sclerosis (Dennett et al., 2018) and patient with musculoskeletal conditions such as shoulder pain (Park and Song, 2017). Web-based exercises are more cost-efficient and

readily accessible (Lewis et al., 2010, Joseph et al., 2014) and therefore has the potential to be used in home-setting continuously, proving their effectiveness (Jahangiry et al., 2017, Foster et al., 2013) and potentially reducing the workload of healthcare service providers (Park and Song, 2017).

Before discussing a web-based intervention for knee OA, one should review the current literature. Eight studies have assessed web-based delivery of exercise intervention for knee pain or knee osteoarthritis (Bennell et al., 2017, Mecklenburg et al., 2018, Lorig et al., 2008, Bossen et al., 2013, Kloek et al., 2018, Brooks et al., 2014, Dahlberg et al., 2016, Nero et al., 2017). The summary of these studies is given in table 1-1.

No.	Author, publication year And location	Study Type	Inclusion Criteria	Online	Online + Face to Face Session	X-rays	Sample Size / Average age / Gender	Intervention, frequency/ week and follow-up (FU) time	Primary outcome	Results	Safety Data	Limitations
1.	**Lorig et al. (2008) USA**	RCT	-≥18 years of age -a diagnosis of OA, rheumatoid arthritis (RA), or fibromyalgia -had access to a computer with Internet	X	N/A	Not done	n=855 (433 in intervention group) Age: 52.2 ± 10.9 yrs intervention group Gender: 89.8% female	Aerobics exercise, stretching and strengthening exercises, three times / week FU: 6 months and 12 months	Six outcome measures : Pain, fatigue, activity limitation, health distress, disability, and self-reported global health	At 12-month FU, intervention group reported improvement on: Pain, activity limitation, health distress, and self-reported global health	Data on adverse event not reported/ provided	-Participants had osteoarthritis (63.9%), rheumatoid arthritis (27.8%) or fibromyalgia (51.6%) (not specific to knee OA) -Blinding was not possible. -population was very heterogeneous for disease, age, education, and symptom distribution.
2.	**Bossen et al. (2013) Netherland**	RCT	-Self-reported knee and/or hip OA -50-75 years of age -Self-reported inactivity -Ability to access the Internet weekly -no contra-indications to	X	N/A	Not done	n=199 (100 in intervention group) Age: 61±5.9 yrs intervention group	Participant's favourite recreation activity-termed as 'Join2move', suggested to do on daily basis. Initially 9-week intervention and then	-Physical Activity using Physical activity scale for the elderly (PASE) -Pain was secondary measure	-At 3- & 12-month FU, PA scores in the intervention group increased 1% & 6% respectively compared to baseline.	No Adverse event reported	-No X-rays -Lack of exercise and participant' favourite recreational activity done -Participants had knee and hip OA -15.6% drop out after 3 months and 24.6% after 12 months.

No.	Author, publication year And location	Study Type	Inclusion Criteria	Online	Online + Face to Face Session	X-rays	Sample Size / Average age / Gender	Intervention, frequency/ week and follow-up (FU) time	Primary outcome	Results	Safety Data	Limitations
			exercise without supervision				Gender: 60% female	continuation of it. FU: 3 months and 12 months	assessed on NRS	-Pain was less (1-unit NRS) at 3-month FU, however no difference at 12 months FU b/w groups.		-Study was not powered for NRS (secondary outcome)
3.	**Brooks et al. (2014) USA**	Pilot study	-≥25 years of age -living independently -walk without walking aid -access to computer with internet	X	N/A	X	n=65 (52 completed study) Age: 61.0 ± 9.4 yrs Gender: 48.1% female	Based on Therapeutic Exercise Resource Centre (TERC) which consisted of strength, flexibility, and aerobic exercises, performed five times / week FU: 8 weeks	WOMAC	All three subscales of WOMAC showed reduction	Data on adverse event not reported/ provided	-No control group -Small sample size -Lacking participants with severe OA
4.	**Dahlberg et al. (2016) Sweden**	Pilot study	Not clearly documented and mentioned 'recruited participants having clinical	X	N/A	Not done	n=53 (36 completed 6-week intervention)	Exercises by joint academy, individualised exercise for lower limb,	Pain (NRS)	11% reduction in pain (NRS) at 6 weeks FU when	Data on adverse event not reported/ provided	-Not RCT -Small sample size & only 68% of recruited participants completed 6

No.	Author, publication year And location	Study Type	Inclusion Criteria	Online	Online + Face to Face Session	X-rays	Sample Size / Average age / Gender	Intervention, frequency/ week and follow-up (FU) time	Primary outcome	Results	Safety Data	Limitations
			OA according to national guidelines & reference to Swedish website for clinical OA is invalid when assessed.				Age: 57.0 ± 14 yrs Gender: 73.6% female	performed on daily basis FU: 6 weeks Additional FUs at 12, 18 & 24 weeks		compared to baseline. 47% reduction in NRS at 24 weeks FU when compared to baseline.		weeks intervention. -No X-rays -Online recruitment and population used to online medium.
5.	**Nero et al. (2017) Sweden**	Observational Quasi-Experimental Study	Not clearly documented. 'used the questionnaires to secure a clinical diagnosis of OA' is documented.	X	N/A	Not done	n=350 (250 completed intervention) Age: 60.8 ± 6.5 yrs Intervention group Gender: 68.3% female	Exercises by joint academy, individualised exercise for lower limb, performed on daily basis FU= 6 weeks	Pain (NRS)	Reported difference of 1.3 units improvement on NRS at 6 weeks FU (P <.001).	Data on adverse event not reported/ provided	-Not RCT -71% completed 6 weeks intervention. -No X-rays -Online recruitment and population used to online medium.

No.	Author, publication year And location	Study Type	Inclusion Criteria	Online	Online + Face to Face Session	X-rays	Sample Size / Average age / Gender	Intervention, frequency/ week and follow-up (FU) time	Primary outcome	Results	Safety Data	Limitations
6.	**Bennell et al. (2017) Australia**	RCT	-≥50 years of age -knee pain >3 months -Knee pain during walking (≥4/10 on NRS) in last week. ->20 out of 68 on the physical function subscale of WOMAC (mild-moderate physical dysfunction -access to computer with internet	X	N/A	Not done	n=148 (74 in intervention arm) Age: 62.0 ± 10 yrs Gender: 58% female in intervention group	Strengthening exercises including knee extensors/ flexors, hip abductor, and calf muscles, three times per week -Control group had educational intervention similar to intervention group but no exercises. FU= 3 months & 9 months	Pain (NRS) when walking	Intervention group reported significantly more improvement in pain (mean difference, 1.6 units on NRS) at 3 months FU. 1.1 units difference on NRS reported at 9-month FU	26/65 participants reported increase knee pain (n=15), muscle soreness (n=5), pain in other area (n=5), and swelling (n=1)	-Study done on chronic knee pain and not knee OA -No X-rays -Participants were not blinded to treatment -No clinical examination -$50AUD gift vouchers were incentive for completing study -Could no establish minimum number of online skype session for clinical effectiveness -Participants in intervention group had higher educational level

No.	Author, publication year And location	Study Type	Inclusion Criteria	Online	Online + Face to Face Session	X-rays	Sample Size / Average age / Gender	Intervention, frequency/ week and follow-up (FU) time	Primary outcome	Results	Safety Data	Limitations
7.	**Kloek et al. (2018) Netherland**	RCT	-40-80 years of age -Hip/knee OA according to the clinical criteria of the American College of Rheumatology -	N/A	X 5 face to face session	Not done	n=208 (109 in intervention group) Age: 63.8 ± 8.5 yrs in intervention group Gender: 67.9% female in intervention group	Strength and stability exercises for hip and knee three times / week for 12 weeks. Also, participant's chosen physical activity (cycling or walking) was gradually increased-recommended frequency not documented by authors. Control group was receiving face to face physiotherapy. FU= 3 & 12 months	Knee Injury and OA Outcome Score (KOOS) and Timed up and go score	No significant differences in primary outcomes between the intervention group and the usual physical therapy group were found at 3- & 12-months FU.	Data on adverse event not reported/ provided	-Not entirely online as there is face to face component. -No X-rays -No clinical examination -Hip & knee joints are included -15% dropout after 3 months and 35% after 12 months -Intervention group consistent of more people with a lower level of education at baseline.

No.	Author, publication year And location	Study Type	Inclusion Criteria	Online	Online + Face to Face Session	X-rays	Sample Size / Average age / Gender	Intervention, frequency/ week and follow-up (FU) time	Primary outcome	Results	Safety Data	Limitations
8.	**Mecklenburg at al. (2018) USA**	RCT	-≥18 years of age -Knee pain for at least 1 month in last 12 months -Participating in the collaborating employers' health plans	X	NA	Not done	n=162 (101 in intervention group) Age: 46 ± 12 yrs in intervention group Gender: 43% female in intervention	Sensor-guided local muscle strengthening and stretching called as 'Hinge health digital care pathway' performed three times / week for 12 week. Control group received 3 education pieces regarding self-care for chronic knee pain. FU= 12 week	Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale (KOOS-PS).	Intervention group had a significantly greater reduction in KOOS Pain compared to the control group at the end of the program (reduction of 7.7 units on KOOS-PS)	Reported no Adverse event	-Study conducted on chronic knee pain sufferers and not on knee OA. -X-rays and clinical assessment were not performed. -studied short term benefits (12 weeks) and no long-term FU

Table 1-1: Studies on Internet / web-based exercises for knee OA or pain till date. <u>Abbreviations:</u> FU, follow up; **KOOS,** Knee Injury and OA Outcome Score**; n,** participants**; NRS,** Numerical Rating Scale**; RCT,** Randomised controlled trial; **WOMAC,** The Western Ontario and McMaster Universities Osteoarthritis Index

The first study was done on participants with knee OA, rheumatoid arthritis, and fibromyalgia, which means that the findings of this study cannot be generalised on knee OA population (Lorig et al., 2008). This leaves us with only seven studies that are done on knee pain or knee OA. Although the results and limitations of these studies are documented in table 1-1 comprehensively, however, I will summarise few issues with each study here.

The second study relied on favourite physical activity of participants, and no standard set of exercises was provided to participants (Bossen et al., 2013). The primary outcome measure was physical activity (self-reported), and the study was not powered for NRS. NRS was a secondary outcome in this study. Also, a difference in NRS was seen at three months (1-unit less on NRS), but no difference was seen at 12 months follow up.

The third study was the only study that included knee x-rays, but it was a pilot study with small sample size. Their primary outcome was WOMAC subscales. Their results showed a reduction on all three subscales of WOMAC at 8-week follow-up. They did not include participants with severe OA; therefore, the findings of this study can be generalised to patients with mild-moderate knee OA only.

The fourth study is another pilot study with a relatively small sample size (n=53) and used the same exercise intervention which is used in iBEAT-OA RCT (Dahlberg et al., 2016). They had NRS as a primary outcome and did not consider doing x-rays. Although they reported 11% reduction in pain at six weeks follow-up, only 68% of recruited participants (n=53) completed six weeks of intervention. Additionally, data on adverse events were not reported.

The fifth Study is an Observational Quasi-Experimental study based on the same intervention which is used in iBEAT-OA RCT (Nero et al., 2017). They used NRS as a primary outcome and reported a reduction of 1.3 unit NRS at 6-weeks follow-up. Inclusion criteria are not defined clearly, and 71% of recruited participants (n=350) completed this study. Data on adverse events were not reported.

The sixth study is RCT conducted on individuals who suffered from chronic knee pain; therefore, findings cannot be generalised to knee OA (Bennell et al., 2017). Their primary outcome was NRS when walking. The intervention group reported significantly more improvement in pain (1.6 units on NRS) at three months follow-up. They awarded 50 Australian dollars as an incentive, and the compliance rate was excellent (89% in the intervention group). No knee radiographs were taken, and they could not establish the minimum number of online skype sessions required for clinical effectiveness. Lastly, participants in intervention group had higher educational levels.

The seventh study was not fully online and had five face to face sessions in addition to online components (Kloek et al., 2018). Their control group was getting face to face physiotherapy; therefore, this study compared two interventions. Primary outcomes were Knee Injury and OA Outcome Score (KOOS) and Timed up and go (TUAG). They had high dropout rates (15% dropout after three months and 35% after 12 months). The pain was not the primary outcome, and the study failed to show any between-group difference in primary outcome at 3 and 12 months follow up. All these limitations and no benefit between partial online treatment versus face to face control arm treatment did not help much to form a basis for future studies, other than

potentially implying that a partial online exercise programme might be as good as face to face intervention.

Eight and last study was again done on chronic knee pain and not on knee OA (Mecklenburg et al., 2018), which is a limitation of this study. Thye used pain sub-scale of KOOS similar to the seventh study and reported a reduction of 7.7 units of pain subscale of KOOS between-group difference at 12 weeks follow up. Radiographs were not done in this study.

To summarise, most of these studies recruited patients with knee pain, and radiographic evidence of knee OA was only assessed in one study (Brooks et al., 2014). This study was a pilot study with a small sample size and lacked a control group. Only five studies in table 1-1 were RCTs on internet-based interventions (Lorig et al., 2008, Bossen et al., 2013, Bennell et al., 2017, Kloek et al., 2018, Mecklenburg et al., 2018). One of these RCTs included rheumatoid arthritis and fibromyalgia other than knee OA (Lorig et al., 2008), leading to only 4 RCTs with chronic knee pain or knee OA patients. Out of these remaining four studies, only one study had NRS as the primary outcome (Bennell et al., 2017); therefore, the study was powered for NRS. However, they recruited patients with knee pain but not specifically with knee OA. A recent study has reported that only 74-80% of participants recruited with chronic knee pain had knee OA (Mecklenburg et al., 2018) based on American College of Rheumatology (ACR) criteria for knee OA (Altman et al., 1986). This study required 74 participants to achieve 80% statistical power to show a difference in pain on NRS (Bennell et al., 2017); however, recruiting sufferers of chronic knee pain reduces that statistical power further by 20% if we were to focus only participants with knee OA. This study becomes short of statistical

power, as removing 20% of 74 participants recruited in this study (assuming that they had knee pain due to non-OA related conditions) would reduce its anticipated statistical power. This in itself can be a limitation of this study (Bennell et al., 2017).

This unit summarises that there is a lack of robust studies on internet-based intervention for knee OA as most studies mentioned above had some methodological flaws or limitations. Hence, there is a need for an exercise programme that is specific to OA.

1.11 Study Rationale

There are no standardised exercises for knee OA in the United Kingdom. Versus Arthritis (previously known as Arthritis Research UK) recommends knee exercise for knee pain, which it views as a generic term covering soft tissue injuries (VersusArthritis, 2021). General practitioners (GPs) usually recommend an exercise regimen as the first line of protocol when consulting someone with arthritis-related knee pain. If exercise intervention fails to impact positively on pain perception, patients are referred for physiotherapy. After a comprehensive assessment by physiotherapists, various exercise interventions are usually prescribed that vary in exercise modality, intensity, and duration, but with variable success in terms of outcome. Therefore, there is a need for standardised exercise interventions to address knee OA pain, ideally accessible online, to maximise efficacy testing and cost-effectiveness.

Uthman et al. (2014) published a systematic review and network meta-analysis and concluded that an intervention combining strengthening exercises with flexibility and aerobic exercise is most likely to improve outcomes of pain and function in knee OA sufferers. They reported that further trials of exercise versus no-exercise are unlikely to overturn this positive result. Unfortunately, they did not include online intervention for knee OA. By that time, only one RCT covered online intervention for knee OA (Bossen et al., 2013), and the intervention in that study consisted simply in participant's favourite recreational activity rather than a programme with an actual set of exercises. While the statement by Uthman et al. (2014) statement that 'further trials are unlikely to overturn this positive result' may appear true, their findings cannot be generalised to an online intervention for knee OA. Hence, there is a need for knee OA studies based on online interventions.

The intervention I carried out was designed to explore the benefits of an internet-based exercise programme in patients with knee OA to establish if a six-week intervention would reduce pain perception. Pain presented by patients with knee OA vary substantially and often do not correlate with the severity of joint changes observed radiographically (Bedson and Croft, 2008). Several recent studies have explored the existence of altered pain processing in knee OA, potentially explaining the variation in pain, but the precise mechanisms underlying pain sensitization in OA remain vague (Courtney et al., 2012, Fingleton et al., 2015). There is currently no gold standard measure to assess and detect the existence of pain sensitization in humans (Woolf, 2011). A frequently used assessment technique is quantitative sensory testing (QST), which involves assessing sensitivity to noxious or innocuous stimuli using

standardized mechanical, thermal and/or electrical test modalities (Pavlaković and Petzke, 2010, Suokas et al., 2012). A systematic review and meta-analysis reported that pain sensitisation is present in people with knee OA (Fingleton et al., 2015). Pain sensitisation is further covered under section 2.12.1. QST / Pain sensitisation is not repeated here to avoid duplication. I want to investigate whether a 6-week online intervention reduces pain perception/ sensitisation in the intervention group.

Knee OA pain is accompanied by several additional disturbances that influence an individual's health. There is a well-known link between sleep disturbances and chronic pain. Both epidemiological studies (Wilcox et al., 2000, Power et al., 2005, Smith et al., 2009a) and experimental studies (Campbell et al., 2015, Harrison et al., 2003, Doherty and Smith, 1993, Leigh et al., 1988) have established a link between disturbed sleep and painful knee OA. These studies confirmed that individuals with OA have higher suffering of sleep disturbances. Sleep disturbances have been recognised as an essential factor in determining pain perception in individuals (Campbell et al., 2015). A relationship between sleep disturbances and pain severity in knee OA patients is usually explored, and sleep disturbances such as shortened sleep duration and fragmented sleep (Wilcox et al., 2000) have been associated with increased sensitivity to pain in OA patients and consequently with decreased quality of life (Smith et al., 2009a). My thesis aimed to establish whether a 6-week digital exercise intervention could also improve sleeping directly or reduce pain leading to improved sleep.

Two critical goals for knee OA pain are relieving pain and reducing disability by improving functional abilities (Uthman et al., 2014). The summary of previous

trials assessing the efficacy of exercise programmes and online exercise intervention to improve functions is covered under 5.1.1 and 5.1.2. It has been discussed in chapter 5 to keep the integrity of that chapter, and we are not repeating it here to avoid duplication. I want to explore whether a 6-week online intervention improves functions other than reducing pain and potential improvement in sleeping habits.

As discussed above and under subheadings 1.5-1.9, exercise intervention effectively reduces and manages pain associated with OA. Some of the issues influencing health-related outcomes of OA, such as inflammation, muscle strength, and sleep quality, can be controlled by exercise. My thesis aims to investigate the role of a standardised online exercise intervention on these related health factors. Here are few reasons given as to why I wanted to do this study and what I wanted to cover in our research, which previous studies struggled to cover:

- There are no RCTs conducted in the UK studying the benefits of online-based exercises for knee OA. There is a potential gap in the provision of health-related services to knee OA and assessing the effectiveness of such online programs.
- I wanted to study exclusively an ‘online’ programme, with no need for face to face physiotherapy being delivered. As per table 1-1, only six studies had a solo online programme for knee OA; however, they had other methodological flaws, as mentioned in section 1.10 and table 1-1.
- There have been a few studies done on Joint academy (JointAcademy, 2021), including a pilot study, qualitative studies, prospective cohort study and observational quasi-experimental study (Dahlberg et al.,

2016, Nero et al., 2017, Dahlberg et al., 2020, Cronström et al., 2019c, Cronström et al., 2019b, Cronström et al., 2019a); however, there have been no RCTs performed on this intervention. RCT is considered a gold standard (Akobeng, 2005, Hariton and Locascio, 2018) which I wanted to conduct in order to reduce biases and provide a rigorous cause-effect relationship for the online intervention.

- The main reason for carrying out x-ray assessments as part of the study was that the objective of my dissertation was to assess if the online Joint Academy programme (JointAcademy, 2021) derived from a safe tested face to face intervention was effective specifically for knee OA pain and not for any form of 'chronic knee pain' which is a broader term including other soft tissue injuries and/or patellofemoral joint syndrome. I wanted to recruit only participants whose radiographs showed knee OA instead of participants with any chronic knee pain. A previous study has documented that only 74-80% of participants recruited with chronic knee pain had knee OA (Mecklenburg et al., 2018) based on American College of Rheumatology criteria for knee OA (Altman et al., 1986). This is relevant as recruiting participants with chronic knee pain could potentially reduce the statistical power of our calculations and if we want to generalise our results on the sufferers of knee OA. Recruiting only participants with knee OA might be seen as a limitation of our study as findings of our study apply only to individuals who have clinical and radiographic evidence of knee OA as opposed to generalising it on the broader population suffering from 'chronic knee pain'.

- A second reason for acquiring knee radiographs was to have participants with mild to severe knee OA and having grades 1 – 4 Kellgren and Lawrence system (K/L) radiographic scores so that the findings from this study could be generalisable to different severities of knee OA. Only one study assessing online intervention for knee OA had previously considered knee radiographs (Brooks et al., 2014). They did not include participants with severe knee OA, thus limiting the generalisation of their findings to mild-moderate knee OA only.
- One of the inclusion criteria was 'accesses to the internet'. The research team purchased several tablets and installed the Joint Academy app as a backup just in case some of the participants did not have access to a smartphone/tablet. I took this decision as I wanted to be able to include participants who were not necessarily digitally savvy. This was to reduce a potential bias of including only those participants who were familiar with the digital world/phones/tablets, having enrolled individuals who were not familiar with using smartphone apps who yet completed the study with help.
- The Nottingham Biomedical Research Centre funded my PhD, hence the mechanistic emphasis of my study with the aim to also understand the complex relationship between Knee OA, pain, quantitative sensory testing (QST), sleep, and physical functions and if there was any link between any of these outcome measures. Therefore, those secondary outcomes were included in this study. There has been no study to date, which tried to look at all these variables while studying online intervention.

- While pain (NRS) and questionnaires such as The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), The Pittsburgh Sleep Quality Index (PSQI) are subjective measures described by participants, I wanted objective data on these to assess whether the objective data back up the subjective findings. Therefore, QST (pain), 30 sec sit to stand, Timed up and Go test (both related to physical functions reported on WOMAC) and actigraphy to assess sleep (related to PSQI) were introduced.

This study is novel as to the best of my knowledge, no study has yet evaluated a web-based intervention to improve knee OA in the United Kingdom, particularly, as I planned to recruit only those individuals presenting with radiographic evidence of knee OA that would rule out non-OA causes of knee pain such as soft tissue injury or patellofemoral syndrome. Therefore, the results from my study potentially help in the generation of recommendations for patients suffering from knee OA.

1.12 Rationale for using online intervention – Joint Academy

The exercise intervention which I used in this project is called 'Joint Academy' (JointAcademy, 2021). It is a web-based program derived from their face to face Supported Osteoarthritis Self-Management Programme (SOASP), developed in Sweden. In the SOASP, evidence-based information and exercise intervention for OA was put into clinical practice. From January 2008

until January 2017, around 75,000 patients participated in the SOASP, 2339 physiotherapists and occupational therapists were educated to deliver the Supported Osteoarthritis Self-Management Programme. Today, SOASP is offered in 700 centres across Sweden (BOA). This intervention has been rated from good to very good by 94% of patients at managing their OA related pain and has an excellent safety profile and acceptability (Thorstensson et al., 2015). Our study will be based on an app / web-based programme, a digital version of SOASP consisting of knee and hip strengthening exercises, functional activities such as sit to stand, step climbing and educational sessions on OA, healthy diet, and weight management. An itemised detail of the programme is not described here as Joint Academy wants to keep detailed contents confidential to avoid replicating their app and programme.

Previous studies have been done in Sweden; however, no work has been done in the UK or outside of Sweden. The results of their pilot study were published in 2016 (Dahlberg et al., 2016) and following that, the results of the observational quasi-experimental study were published in 2017 (Nero et al., 2017). Both studies showed promising results; however, some limitations have already been discussed under section 1.10 and in Table 1-1 as 4th and 5th studies. Following these two studies, they published patient satisfaction in qualitative studies (Cronström et al., 2019a, Cronström et al., 2019b) and a prospective cohort study (Cronström et al., 2019c). The prospective cohort study was based on 458 participants (mean ± SD age 62 ± 5.6 years, 67% women) with hip and knee OA diagnosis and were evaluated after six weeks of Joint Academy intervention. Outcome measures were joint pain, health-related quality of life (the EuroQol 5-domain [EQ-5D] questionnaire), walking

difficulties, the 30-second chair stand test, and willingness to consider surgery and were collected at baseline and six weeks. At follow-up, 31% of those participants willing to consider surgery at baseline no longer considered surgery (OR 0.67–1.64; P < 0.05) with less pain and higher EQ-5D score at six weeks. There were few limitations, though. Their participants were with hip and knee OA with different expectations of surgery and different surgical outcomes. Thus, separate analyses may be warranted; however, their post hoc analyses showed no difference in baseline pain and function or willingness to consider surgery between those participants with hip and knee OA. Another limitation was the willingness to consider total joint replacement, and it was evaluated after six weeks only. The long-term desire for total joint replacement for this programme has not been assessed as of yet.

Additionally, they have published a longitudinal cohort study reporting the benefit of Joint Academy after 24 and 48 weeks of treatment (Dahlberg et al., 2020). They had 499 participants for 0-24 weeks follow up and 138 participants for 0-48 weeks follow-up. For the 24-week sub-sample, pain NRS decreased monthly by -0.43 units (95% CI -0.51 to -0.35, mean knee pain from 5.6 to 3.1) and 30-second sit to stand repetitions increased monthly by 0.76 repetitions (95% CI 0.64 to 0.89, mean for knee from 10.0 to 14.3). For the 48-week sub-sample, pain decreased monthly by -0.39 units (95% CI -0.43 to -0.36, mean knee pain from 5.7 to 3.2), and repetitions increased by 0.72 (95% CI 0.65 to 0.79, mean repetitions for knee from 10.3 to 14.4). This was not an RCT which lacked a control group and no randomisation leading to assess the

mechanisms of the observed reduction in pain and increased physical function in these OA patients.

There has been a cost-analysis study on Joint Academy as well, and they reported that overall the digital model costs around 25% as much as the existing face-to-face model of care (Ekman et al., 2020). Again, there are some limitations to this study. First and foremost, their analysis was based on retrospective data, whereas data from RCT would be at a lower risk of bias. Additionally, this cost analysis is assessed for Sweden; therefore, generalisation to other countries will require further confirmation or additional studies. Lastly, they did not factor in the actual costs of any technical support for Joint Academy (a cost of background technical issues to the company running this). However, if this programme has to be run by the government, additional technical charges should be considered for a comprehensive cost analysis.

Our study trial started in 2018, and by that time, only a pilot study (Dahlberg et al., 2016) and an observational quasi-experimental study (Nero et al., 2017) were published. I was unaware of any further studies on their exercise intervention, and to date, they have not yet carried out any RCT, although a protocol for RCT has been published (Nero et al., 2018).

In addition to the factors and the scientific literature mentioned above for Joint Academy, there are few other reasons as to why I selected Joint Academy:

- Three years for PhD was a short time to put together an online exercise plan and develop an app. Whereas Joint Academy was already established and fully functional programme at the time. These time

restrictions and an already developed app led to using the Joint Academy (JA) app.

- They had an excellent safety profile which was established from the literature mentioned above.
- They had excellent patient satisfaction, as mentioned above.
- There was no direct competitor, which provided exclusive online exercises at the time. Other programmes such as ESCAPE (Hurley et al., 2012) and GLA:D (Skou and Roos, 2017) had a face-to-face component followed by an online programme.
- They allowed us to use their app for research purposes.

To make it easier for readers, I will call this online intervention as Joint Academy (JA) and this randomised controlled trial (RCT) as internet-based exercises aimed at treating knee OA (iBEAT-OA).

1.13 Objectives of Study

1.13.1 Primary Objective

To test whether 6-week internet-based exercise intervention can reduce pain perception in knee OA. This will be done using the 0-10 Numerical Rating Scale (NRS) pain.

1.13.2 Secondary Objectives

To test whether 6-week internet-based exercise intervention can improve sleep disturbances, functional abilities and reduce pain sensitisation.

To assess if pain relief from exercise correlates with improvements in sleep quality.

Chapter 2 Methodology

2.1 Trial Design

iBEAT-OA was a randomised controlled trial in the primary care setting at Nottingham with participants suffering from knee arthritis, 1:1 randomised to web-based exercises or usual care.

2.2 Ethics

The sponsor approved the study, Research Ethical Committee (REC) (ref: 18/EM/0154), Health Research Authority (HRA) (protocol no: 18021) and the Nottingham University Hospitals NHS Trust Research & Innovation (R&I) department (ref: 18RH004).

2.3 Protocol for Study

The protocol for the study was published in BMJ Open (Gohir et al., 2019) and highlighted most of the aspects which are covered in this chapter.

2.4 Training

The author (SG) is a qualified physiotherapist with more than 15 years of experience in physical assessments and completed most assessments conducted for this study. SG is a trained musculoskeletal sonographer and interventionist who had done more than 250 supervised scans during his training to become a sonographer and thousands of independent ultrasound

scans as part of his clinical work before conducting this study. Furthermore, being an advanced physiotherapy practitioner means he assesses and infers x-rays routinely in his clinical practice.

SG and research nurse (TK) completed an introduction to good clinical practice in 2018 and achieved their research passports before starting the trial.

2.5 Intra and Inter-observer reliability

Based on the training of the study assessor (SG), following reliability assessments were planned.

2.5.1 X-rays

Intra-observer reliability in reading knee x-rays (standing posterior-anterior) was tested for the study assessor (SG) by assessing 20 x-rays on two separate days within five days.

Inter-observer reliability was tested against a senior research fellow with clinical expertise in reading x-rays. Twenty x-rays were compared. Both investigators were blinded to previous measures and each other's measurements.

2.5.2 Quantitative Sensory Testing (QST)

Quantitative Sensory Testing (QST) comprises non-invasive psychophysical validated methods that use different stimuli of increasing intensity to measure somatosensory perception, based on responses of the subject (Attal et al., 2013, Huet et al., 2018, Hansson et al., 2007). These methods are based on

the measurements of responses (i.e., non-painful sensations and pain) to thermal, mechanical and vibration stimuli, the intensity of which is controlled by automated devices (Attal et al., 2013, Bouhassira, 2019). The main advantage of QST over more traditional evaluation methods is that they can be used to quantify various types of somatosensory discrepancies and allodynia or hyperalgesia subtypes (i.e., in response to pressure or brushing, heat or cold) (Bouhassira, 2019). QST used in our study is explained further under sub-section 2.12.1.

For this study, inter-observer reliability was tested against a colleague assessor. This was done on 15 healthy volunteers. Both investigators were blinded to each other's measurements.

Intra-observer reliability in QST was tested for the study assessor (SG) by running QST on five healthy volunteers on two separate days within five days.

2.6 Participants

A selection of eligible people for the study were invited from existing databases held at Academic Rheumatology, City Hospital Nottingham, of participants with knee pain who had agreed to be contacted for future studies. The eligible people were men and women, aged between 45 and older, registered with the GP surgery. The screenings of existing records were done by research team at Academic Rheumatology. All suitable individuals for the study were sent a participant information sheet (PIS) (Appendix 1). It was done to allow participants to think about the research and their involvement in this study.

2.7 Inclusion Criteria

1. Aged 45 years and above.
2. Clinical diagnosis of knee OA with complaints of knee pain for ≥3 months, early morning stiffness <30 minutes, crepitus, bony tenderness, and no palpable warmth and radiographically established OA (at least score 1 on K/L scale)
3. Able to read and write English
4. Able to use/access computer or tablet and have access to the internet

2.8 Exclusion Criteria

1. Inability to give informed consent – (capacity levels are already established under GP care)
2. Terminal or mental illness
3. Neurological conditions (Stroke, Multiple Sclerosis, Parkinson's, Motor Neuron Disease, Muscular Dystrophy, Huntington's disease), inflammatory joint diseases including rheumatoid arthritis, gout or calcium pyrophosphate deposition disease (CPPD), and dementia

4. Participants with sleep apnea previously diagnosed by a physician
5. Acute soft tissue injury to the knee within last 3 months before recruiting diagnosed by a physician
6. Unstable heart condition or rapid fluctuations in hypertension previously diagnosed by a physician.
7. BMI>50 as they would benefit from 1:1 sessions.

Most participants for this study were recruited from a database held at the University of Nottingham. These participants took part in previous studies and agreed to be contacted for future studies. Based on their earlier radiographs and the information they had provided before, these participants had already been clinically diagnosed with knee OA. Despite this, the research team screened all participants (whether from the database or recruited from word of mouth or social media) to ensure that they complied with inclusion and exclusion criteria. Any medical conditions mentioned in exclusion criteria were self-reported by participants, and if in doubt, SG reviewed their medications. After reviewing their self-reported health condition and medication, if there was ambiguity around confirmed diagnosis or an unstable heart condition, the plan was to write to the general practitioner (GP) asking for diagnostic clarity on pathologies mentioned in the exclusion criteria.

2.9 Recruitment

The department of Academic Rheumatology, City Hospital Nottingham, generated an internal database (from previous cohort studies) of participants who agreed to participate in futures studies. The research team posted these

participants a participant information sheet (PIS). PIS (Appendix 1) suggested interested participants to contact the research team via phone. Individuals who rang were screened over the phone to ensure that they fulfilled eligibility criteria (excluding x-rays at this provisional recruitment stage). This initial screening was done by the research team, who were trained staff and gained verbal consent from interested participants at this stage. If there was any ambiguity around diagnosis or medication, the chief investigator (Dr Ana M. Valdes) or SG were contacted to seek further guidance. If participants fulfilled these criteria, they were booked for face-to-face assessments at Academic Rheumatology.

After initial screening over the phone, those participants who fulfilled study criteria were invited to Academic Rheumatology, City Hospital Nottingham. With the assistance of TK (research nurse), SG greeted these participants during their first visit. SG/TK went through PIS to ensure that all participants' questions were answered, and if participants were happy to proceed, consent forms for this study were signed.

The first face to face interaction was considered as the baseline assessment. The purpose of the visit was to confirm suitability by proceeding with radiographs for those who have not had x-rays in the last 12 months. Those who had x-rays in the previous 12 months and qualified for this study were exempt from x-rays, and they proceeded with the assessment after signing the consent form. Those individuals who had not had x- rays went through the x-rays of their most painful knee. All qualifying individuals (K/L= 1 or above) were randomised to interventional and control groups.

The research team carried out the randomisation so that SG/TK were not aware of the allocation of these participants. In the first two months of initiating this study, interested participants were randomised to either group on the morning of their anticipated session (before their arrival); however, a few participants failed to attend their baseline assessment. The numbers for these participants are shown in the flow chart (Figure 3-1, allocation section as 'did not receive allocated intervention'). Due to the need to provide some participants with a tablet, and therefore to ensure predictability of need for tablets (only used for the treatment arm) randomisation was done using block randomisation as enabled by the sealedenvelope.com software. After two months, the research team decided to randomise participants only if they showed up for the study and signed the consent form. This change was made to avoid wasted expenses while using sealedenvelope.com for randomisation, as explained in section 2.14. Participants were informed about their allocation at the end of their first visit.

It was explained to the participant that entry into the trial was entirely voluntary and that their treatment and care would not be affected by their decision. Participants were informed that they were free to leave the study at any time without giving any reason. In the event of their withdrawal, it would be explained that their data collected so far could not be erased. The participant information sheet and consent form covered the consent to use the data in the final analyses where appropriate. Those participants who did not own a tablet, were allowed to use generic tablets allocated by the research team. Those who withdrew from the study were made aware that this would not in any way affect

their future care. Furthermore, participants could withdraw from ultrasound-guided aspiration, should they deemed it to be uncomfortable.

2.10 Interventions

A web-based exercises platform (Joint Academy®) was used as an intervention given to the treatment arm. The rationale to use this as an intervention and relevant literature on development and effectiveness have been explained in detail in section 1.12, 'Rationale for using online intervention – Joint Academy'. The company behind the digital version gave consent to using the Joint Academy app in this study for free.

The program consists of a mixture of open and close chain exercises, a combination of concentric, eccentric and focusing on the global strength of legs, including the muscles around the hip and knee joints and balance enhancement exercises. The intervention further includes educational sessions integrated into the programme covering the basics of OA, its treatment, self-managing symptoms of OA and the benefits of maintaining a healthy lifestyle. Due to copyright and intellectual property issues associated with the Joint Academy intervention, I am limited as to the amount of detail I can include in my dissertation regarding the intervention. Readers may find further information at https://www.jointacademy.com/gb/en/

Those participants who qualified for the study were asked to sign the informed consent form, and the participants were randomised to the interventional and control groups.

After randomisation, interventional group received a link via email, which was used to register and log in to the digital online portal. After log-in was achieved, participants were asked to answer an online questionnaire covering areas such as joint pain intensity, health-related quality of life, physical function, and being instructed in and performing a physical test assessing lower limb strength and physical function. This questionnaire formed a part of the online baseline assessment. The purpose of this was to establish their baseline fitness and tailoring the exercises according to their fitness level. There were varying difficulty levels by adjusting the repetition of exercises or changing the exercise and involving more muscles involved in exercises. The intervention consisted of a 6-week internet-based physiotherapy program that provided information, exercises, contact details of a personal physiotherapist, education about lifestyle and behavioural changes. Exercises consisted of knee and hip exercises and functional activities such as sit to stand and stair climbing. This intervention could be accessed using a smartphone or a tablet. The program encouraged physical activity, physiotherapy, and self-management by sending e-mail prompts daily to help participants continue during the intervention period. The adherence of the participants was encouraged by these e-mails and monitored manually by SG using the online portal.

There were two face-to-face sessions between participants and physiotherapist/nurse, at enrolment and after six weeks. However, the physiotherapist (SG) was available via asynchronous online chat or phone during the 6-week study period. This means that participants could contact the physiotherapist using their app and by clicking on the button ‘chat to your physiotherapist’. They could type their queries, and these queries were

instantly sent to the physiotherapist (SG). SG monitored this daily and spent approximately 30-90 minutes/week on this asynchronous online chat.

Additionally, the participants were able to ring the physiotherapist on a landline number. They were able to leave a message for SG if this was not during working hours or if SG was conducting assessment sessions. The purpose of this additional support (online or by telephone) was to reassure participants who had additional queries or lacked the confidence to try a new set of exercises.

Once the exercises programme was finished in six weeks, the participants were seen face to face to perform the physical tests and asked to fill in the same questionnaire to enable post-intervention evaluation. These assessments were a replication of the baseline assessments.

After six weeks, participants were allowed to continue with sustain-program for self-management, mainly focusing on the continuation of treatment and performing the exercises regularly; however, no further assessments were taken for the purpose of research.

The control group was advised to continue with their routine self-management offered in the community setup. Baselines and follow-up sessions, and assessments were similar to intervention group. They followed the routine management of knee OA recommended by the National Institute for Health and Care Excellence (NICE), including non-pharmacological and pharmacological management (NICE, 2020).

The PhD candidate (SG) carried out all the assessments and was assisted by a research nurse (TK).

2.11 Outcomes and Hypotheses

All outcome variables were collected at baseline and follow-up in both arms.

2.11.1 Primary Outcome

Pain assessed on Numerical Rating Scale (NRS), perceived average daily pain during the last seven days, reported on a scale 0-10, where 0 is no pain, and 10 is the worst pain imaginable. NRS is a valid and reliable tool to measure pain intensity (Hawker et al., 2011, Alghadir et al., 2018). The previous study has reported high test-retest reliability has been observed in both literate (r = 0.96) and illiterate patients (r = 0.96) with rheumatoid arthritis (Ferraz et al., 1990), although this study was not done on OA patients. A recent study that assessed test-retest reliability, validity, and minimum detectable change (MDC) of visual analogue (VAS), numerical rating (NRS), and verbal rating scales (VRS) for measurement of knee OA pain reported intraclass correlation coefficients (relative reliability) of the VAS, NRS, and VRS as 0.97, 0.95, and 0.93, respectively (Alghadir et al., 2018). This is slightly different reliability reported by another study that compared NRS (r=0.99) and VAS (r=0.97), albeit participants observed in this study were the sufferer of pain from musculoskeletal conditions (Gallasch and Alexandre, 2007). Both studies indicate that reliability for NRS was excellent. Alghadir et al. (2018) also reported the standard error of measurement (SEM) for NRS as 0.48 and minimum detectable change (MDC) as 1.33.

2.11.2 Secondary Outcomes

Following are secondary outcomes. They are mentioned briefly here, and a detailed description is given under section 2.12 (clinical assessments).

- Objective measures of pain sensitivity known as quantitative sensory testing (QST), including Pain Pressure Threshold (PPT), Temporal Summation (TS), and Condition Pain Modulation (CPM). QST was selected as one of the secondary outcome measures to establish whether any improvement or deterioration on NRS is backed up with QST data, or despite any changes on NRS, would participants demonstrate any difference in pain sensitivity post-6-weeks of exercise intervention.
- Inflammatory markers on ultrasound, including synovial fluid, synovial hypertrophy and vascularity. This outcome was selected to see if there was any evidence of sonographic inflammatory markers in knee OA and, if yes, would they reduce after the exercise intervention.
- Maximum Voluntary Contraction (MVC) of quadriceps and hamstrings using a dynamometer. This secondary outcome was selected to assess whether six weeks of exercise intervention would effectively strengthen the knee joint's muscles.
- Muscle thickness assessment of the vastus lateralis on ultrasound. This secondary outcome was selected to see if sonographic features of muscle thickness correlated with the findings of dynamometer assessments (MVC) mentioned above.
- Physical Functions including Timed up and go (TUAG) and 30 Seconds sit to stand (30CST) tests. These functional tests were added as

secondary outcome measures to assess whether participants improved their functions post-intervention.

- Questionnaires including The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), The Pittsburgh Sleep Quality Index (PSQI) and The Musculoskeletal Health Questionnaire (MSK-HQ). These questionnaires were selected to assess how patients perceived their pain, functions, disability and sleeping parameters and if they felt that there were improvements or deteriorations on these parameters.
- Sleep assessed with actigraphy. This was added as one of the secondary outcome measures to determine whether six weeks of exercise intervention had an effect on the sleeping habits of participants.

2.11.3 Hypotheses

- Primary Hypothesis 1: iBEAT-OA exercises will reduce knee pain (NRS) relatively more in exercise group than in the control group.
- Secondary Hypothesis 2: iBEAT-OA will improve objective pain assessment QST in exercises group compared to control group.
- Hypothesis 3: iBEAT-OA will improve maximum voluntary contraction of quadriceps and hamstring in exercise group.
- Hypothesis 4: iBEAT-OA will improve objective functional assessment in exercise group compared to control group.
- Hypothesis 5: iBEAT-OA will improve WOMAC and MSK-HQ scores in exercise group.

- Hypothesis 6: iBEAT-OA will improve sleep quality and quantity in exercise group, including PSQI.
- Hypothesis 7: iBEAT-OA will reduce sonographic features of inflammation (Effusion, synovial hypertrophy and hypervascularity).

2.12 Clinical Assessments

All outcome variables were collected at baseline and follow-up in both arms. The clinical assessments are explained below, and forms used in this study are included in Appendix 2.

2.12.1 Pain (Pressure Pain Threshold – PPT, Temporal Summation – TS, and Conditioned Pain Modulation – CPM)

I used standardised quantitative sensory testing (QST) such as Pressure Pain Threshold (PPT), Temporal Summation (TS) and Conditioned Pain Modulation (CPM). The purpose of using QST was to establish whether these exercises reduced the localised tenderness or global central sensitisation in knee OA sufferers.

The standard procedures for PPT, TS and CPM were used as explained below. Figure 2-1 shows QST sites.

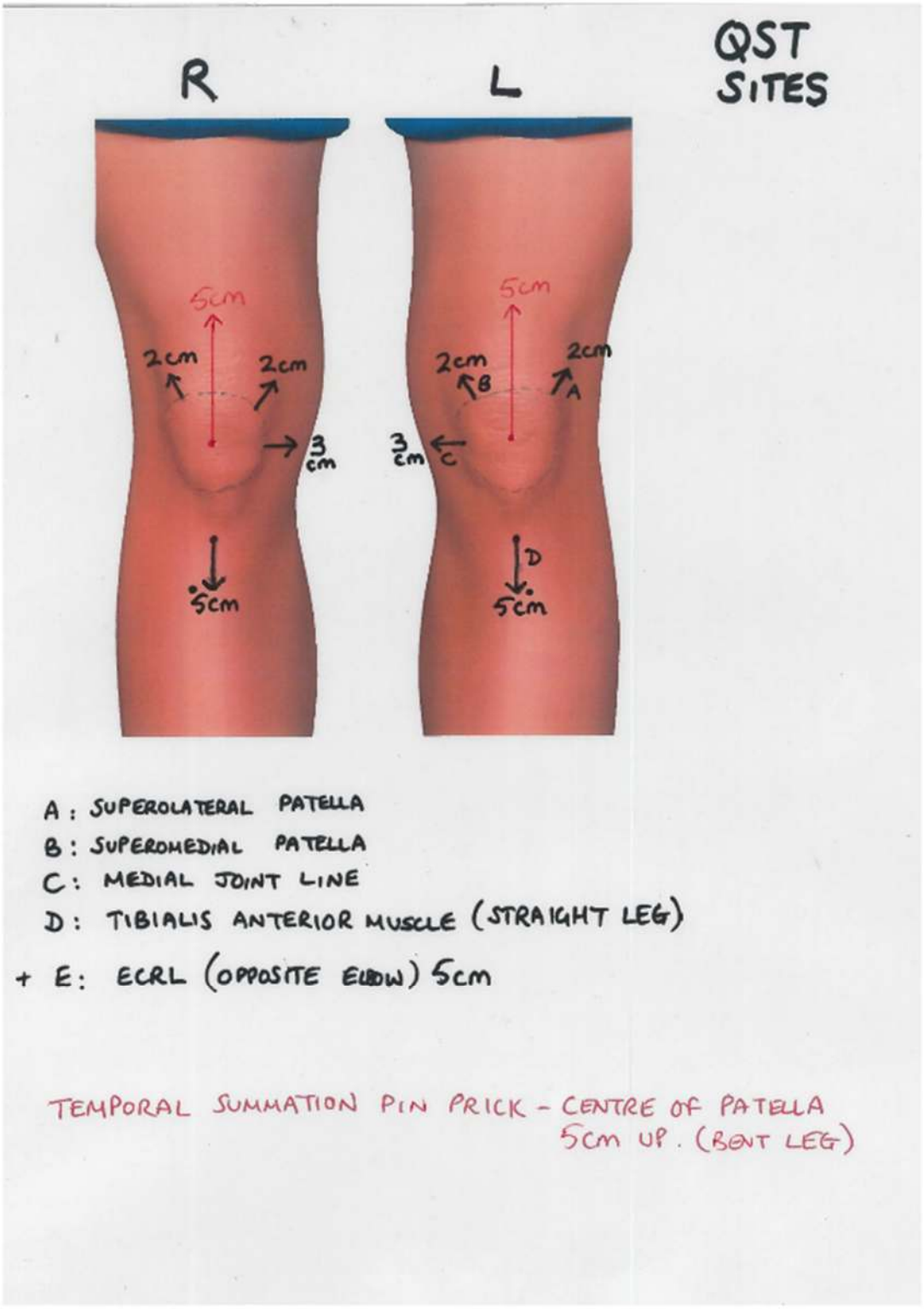


Figure 2-1: Pressure Pain Threshold (PPT) measurement sites over the peripatellar region.

2.12.1.1 Pressure Pain Threshold (PPT)

Pressure Pain Threshold (PPT) is defined as the minimum force applied to the human body which induces pain (Maquet et al., 2004, Goode et al., 2014). PPT is a non-invasive test during which the sensitivities of the nerves are assessed by recording the smallest force applied to the skin. When this force by the skin's surface area is applied (pressure), this will be felt as mild, temporary pain and recorded. PPT readings are inversely related to pressure pain sensitivity, i.e., a lessened PPT indicates increased pain sensitivity (Goode et al., 2014). A recent systematic review including eight studies reported that from a total of 1003 participants (one local and one remote PPT were included making total assessments n= 2006), the point estimate for differences in PPTs between knee OA participants and controls was −0.86 (95% CI −1.09 to −0.62), indicating greater pressure pain sensitivity in people with knee OA ($P < 0.001$) (Fingleton et al., 2015). Their meta-analysis comparing local PPTs between participants with knee OA and controls found that, from 1003 participants, the point difference was −0.97 (95% CI −1.38 to −0.56), indicating greater local pressure pain sensitivity in people with knee OA ($P < 0.001$). They have reported high heterogeneity. PPT has been deemed a valid and reliable method to establish tenderness around the knee joint (Wessel, 1995, Mutlu and Ozdincler, 2015, Gagliese et al., 2005, Middlebrook et al., 2020).

In this study, the pressure probe used consisted of a rod with an end the size of a 5p piece, mounted in a handheld device connected to a computer. The force with which the probe was pressed onto the skin was gradually increased until the participant indicated (by pressing a button) that the sensation had changed from pressure to pain. The probe was then immediately taken off the

skin, and a reading was noted. The probe was used on the knee (medial joint line, supero-lateral, supero-medial and tibialis anterior) using a standardised protocol previously utilised in other studies within the Pain Centre. The participants were familiarised with the test before it was administered so that they knew what to expect and how to respond. The algometer used for this study was AlgoMed by Medoc Ltd. Advanced Medical Care System.

2.12.1.2 Temporal Summation (TS)

Temporal Summation (TS) refers to the experience of increased pain sensitivity in response to repetitive noxious stimuli over time (den Boer et al., 2019). It is a non-invasive test during which repetitive mechanical stimulation is applied over a short period to get their augmented response. Increased TS is a measure of spinal hyperexcitability in which the summation of repetitive C-fibre input produces an increased response (Fingleton et al., 2015, La Touche et al., 2018) and is tested using repeated noxious stimulation. Four studies reported increased facilitation of TS in knee OA participants (Skou et al., 2013, Finan et al., 2012, Arendt-Nielsen et al., 2010, King et al., 2013). Increased pain response to a repeated mechanical stimulus may indicate enhanced central sensitisation. TS has been used in previous studies and is deemed a valid and reliable method (Wylde et al., 2011, Middlebrook et al., 2020).

In our study, the test site was suprapatellar region (5 cm proximal from the central part of the patella). A 256mN weighted pinprick stimulator was used and applied perpendicular to the skin of the suprapatellar region of the affected knee (5cm proximal from the centre of the patella). The participants were asked

to rate the pain or sharpness they experience from 0-10, where 0 indicated no pain or sharpness and 10 indicated the most intense pain or sharpness imaginable. The Numerical Rating Scale (NRS) with verbal descriptors was used. The response of the participants was recorded. The same stimulator at the same site was applied ten times repeatedly at a rate of 1/second. The size of the area was kept approximately 1cm square. At the end of the series of 10 pinpricks, the participant was asked to rate the pain or sharpness (average reading) which they experienced over the whole series of 10 stimuli using the same NRS. The mechanical temporal summation reading was calculated as the difference between two ratings (second rating minus the first rating), and positive values indicated signs of central sensitisation. I used a 256mN weighted pinprick stimulator made by MRC Systems GmbH Medizintechnische Systeme.

2.12.1.3 Conditioned Pain Modulation (CPM)

Conditioned Pain Modulation (CPM) refers to the reduction in pain sensitivity of a tested stimulus due to the interference of a second stimulus ('conditioning' stimulus) which is applied at the same time but to a remote body region (La Touche et al., 2018). CPM is an endogenous pain repressive process compromised in many chronic pain populations (Cathcart et al., 2010, Yarnitsky, 2010). Assessment of CPM involves evaluating a painful test stimulus in the absence and presence of a second painful (conditioning) stimulus applied to a remote site (Lewis et al., 2012, La Touche et al., 2018). CPM paradigms are commonly used to assess the function of endogenous pain inhibitory pathways in humans. In a typically functioning nociceptive

system, the amount of pain experienced with the primary test stimulus will be reduced during the presentation of the secondary conditioning stimulus (Pud et al., 2009, Yarnitsky et al., 2010, Lewis et al., 2012). Two previous studies demonstrated a dysfunctional CPM response in people with knee OA (Arendt-Nielsen et al., 2010, Graven-Nielsen et al., 2012). CPM is reported as a reliable assessment method (Kennedy et al., 2016, Biurrun Manresa et al., 2014); however, some studies suggested limited overall validity (Fernandes et al., 2019, Valencia et al., 2013).

In this study, CPM examination included the use of PPT equipment and PPT testing. The reference point for CPM testing was the tibialis anterior on the most painful knee (same reference point examined in PPT). Verbal instructions were given to the participants, and the procedure was explained. The research team member wrapped a 7.5cm wide tourniquet cuff around the contralateral arm to the knee being tested. The lower rim of the tourniquet cuff was kept 3cm proximal to the cubital fossa. Systolic pressure was set to 20mmHg higher than the systolic blood pressure of the participant. The Numerical Rating Scale (NRS) target of ≥4 out of 10 from the cuff pressure was required before repeating PPT procedure. After the target cuff pressure was achieved, the participant was asked to rate sensation in the arm from 0-10. The participant was asked to make hand grips until NRS of 4 was reached. NRS rating was asked every five hand grips.

Once the NRS of 4 was achieved, the probe of the algometer was applied in the same manner as before to the tibialis anterior site (during PPT testing). Once the participant pressed the button to indicate that the pressure of the algometer was converting into pain, the probe was withdrawn, and the cuff was

deflated and released from the elbow. Participants were advised to wait until cuff evoked pain subsided before re-testing, and a minimum of 1 minute was spared. PPT test was repeated (without the cuff now). Their difference in PPT score (with conditioning – without conditioning) established the CPM effects. A positive value predicts efficient CPM, and a negative value indicates ineffective CPM.

2.12.2 Inflammatory Markers on Musculoskeletal Ultrasound (MSK-USS) – Synovial Fluid, Synovial Hypertrophy and Hypervascularity

I conducted a Musculoskeletal Ultrasound Scan (MSK-USS) on the participants' painful knees to establish if they had inflammation of synovial membrane. There is enough evidence that inflammation is present in all stages of OA (Atukorala et al., 2014, de Lange-Brokaar et al., 2012, Englund, 2008, Loeuille et al., 2005). Synovitis or synovial fluid inflammation is associated with pain, disease severity and progression of OA (Attur et al., 2010, Atukorala et al., 2014). Synovitis manifests as synovial membrane thickening, increased vascularity and/or joint effusion (Atukorala et al., 2014, Hayashi et al., 2011, Keen and Conaghan, 2009, Guermazi et al., 2009). As standard radiographs cannot visualise the synovial membrane, I anticipated using an ultrasound machine. I assessed synovial fluid, hypertrophy of synovium, and Power Doppler (PD) presence during the ultrasound scan. Synovial hypertrophy, synovitis and knee effusion are linked with arthritis in the knee and associated with knee pain in OA (Fernandez-Madrid et al., 1995, Hill et al., 2001, Sokolove

and Lepus, 2013b, D'Agostino et al., 2005, Sarmanova et al., 2017, Sarmanova et al., 2016). PD provides a reliable and accurate method for visualising blood flow in the synovial tissue, and histological findings support the value of this technique (Walther et al., 2001, Labanauskaite and Sarauskas, 2003, D'Agostino et al., 2005). An ultrasound scan is a valid and reliable instrument for assessing synovial disease (D'Agostino et al., 2005, Karim et al., 2004, Sarmanova et al., 2017, Hayashi et al., 2011), and synovitis is strongly associated with OA, as mentioned earlier.

A recent systematic review and meta-analysis investigated the effect of land-based exercise therapy for more than six months on knee effusion and synovitis assessed on MRI scans (Van Ginckel et al., 2019). Low-quality evidence revealed no treatment effect on the odds of change in synovitis (OR: 0.9 [95%CI, 0.51 to 1.60], I^2= 0%) and effusion (OR: 0.88 [95%CI, 1.11 to 3.26], I^2= 0%). This means that long-term exercise therapy did not change effusion or synovitis in people with knee OA. After six weeks of intervention, I wanted to assess whether we saw any difference in knee OA's sonographic features.

I aimed to aspirate the synovial fluid (SF) (subjective to the consent of the participants), and the purpose was to establish if I could assess the synovial fluid to predict the phenotypes strongly associated with osteoarthritis. Studying synovial fluid (SF) biomarkers alongside clinical, radiographic and ultra-sonographic characteristics is one strategy to improve resolution and stratification into targetable OA phenotypes (Snelling et al., 2017).

I used the protocol utilised in an earlier study conducted in the rheumatology department (Sarmanova et al., 2017). The most painful knee was scanned

using a Toshiba Aplio SSA-770A machine with a multi-frequency (7-12 MHz) linear array transducer. The same equipment and software were used during the whole study. The assessment was performed with knee flexion of approximately 20-30° and included the supra-patellar recess, medial and lateral tibio-femoral spaces. USS detected changes were defined according to definitions accepted by the OMERACT-7 Group (Wakefield et al., 2005). This has been shown in Figure 2-2. The maximal synovial thickness and effusion depth were measured in millimetres using the longitudinal axis. These absolute values were dichotomised as absent (<4mm) or present (≥4mm) according to the EULAR Research Group recommendation (D'Agostino et al., 2005). A Power Doppler (PD) assessment focused on areas of synovial hypertrophy. A positive PD signal which provided information on vascularity was recorded as absent or present.

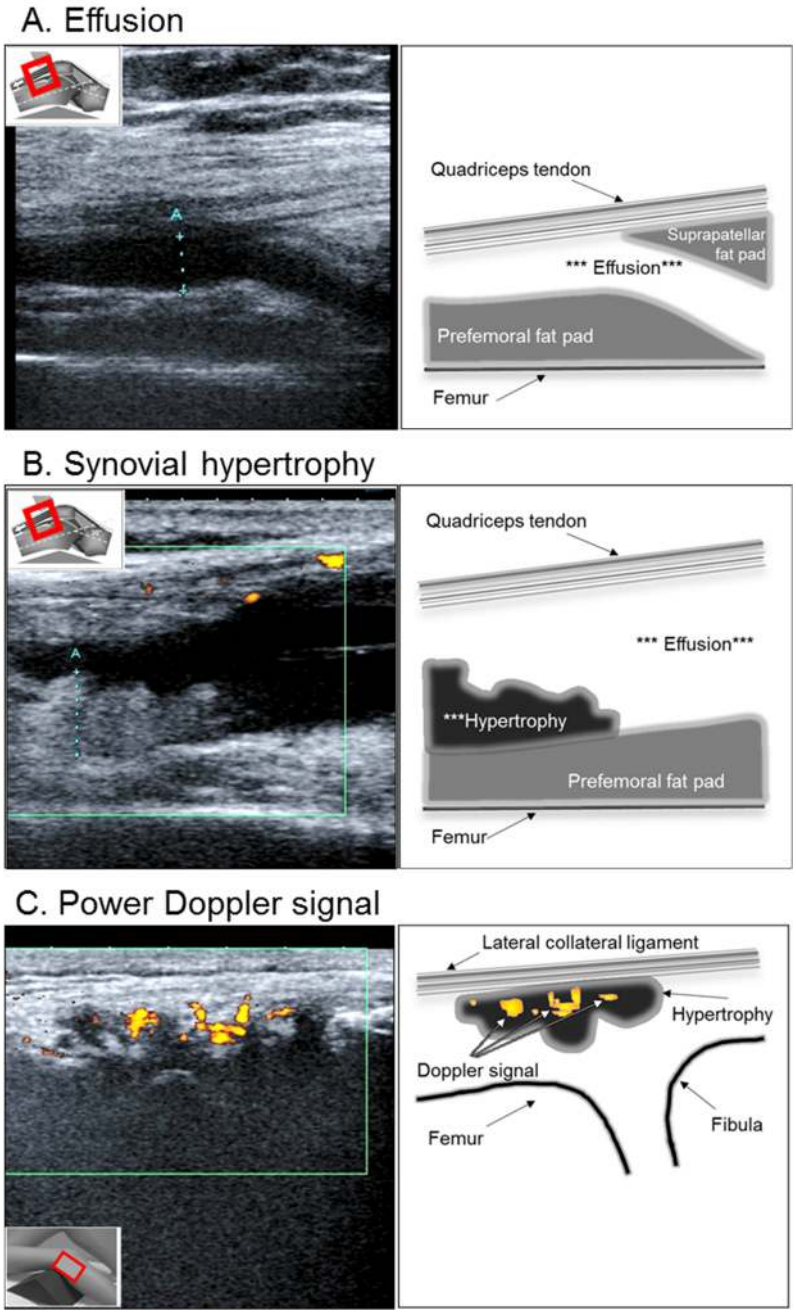


Figure 2-2: Grey-scale US image of an effusion (image A) and synovial hypertrophy (image B) in the supra-patellar pouch, and Power Doppler signal in the lateral tibio-femoral space of the knee (image C). On the left side of these images, the real US images are shown with detected synovial pathology (Sarmanova et al., 2017); images of the knee area and position on the right are schematic drawings of synovial pathology in relation to other joint structures (Bianchi, 2016).

2.12.3 Muscle Thickness Assessment (MTA) of Vastus Lateralis Oblique (VLO) using MSK-USS

I aimed to ultrasound the muscle mass around the knee and assess if six weeks of exercise program resulted in any difference in the muscle mass around the knee. There is conflicting information on atrophy of the muscles around the knee, whether vastus medialis or vastus lateralis atrophies significantly when all four quadriceps muscles have been assessed and compared. It is evident that decreased strength of quadriceps muscles is found in the population suffering from knee arthritis (Hassan et al., 2001, Heiden et al., 2009, Hurley et al., 1997, Lewek et al., 2004, Slemenda et al., 1997). One study suggested that all four muscles of knee extensors atrophy similarly in the elderly population (Trappe et al., 2001). Another study reported atrophy of type 2 fibres in the vastus lateralis and associated it with OA compared to the control group (Nakamura and Suzuki, 1992). Other studies have associated atrophy of vastus medialis with arthritis (Fink et al., 2007, Ikemoto-Uezumi et al., 2017) and greater vastus medialis cross-sectional area is associated with reduced knee pain and reduced medial tibial cartilage loss (Wang et al., 2012). A recent study has studied the sonographic changes of vastus lateralis after introducing exercises and correlated the findings to the MRI scan, and they conclude that ultrasound is a valid method of assessing muscle thickness (Franchi et al., 2017). This study has used vastus lateralis muscle to conclude these findings, and therefore I planned to measure vastus lateralis muscle mass thickness and pennation angle as described in earlier studies (Strasser et al., 2013, Franchi et al., 2017). The pennation angle is defined as the angle between muscle fibres and the deep fascia of the muscle (Strasser et al., 2013). The pinnation

angle correlates with the maximum voluntary contraction (MVC) force which is a measurement of muscle strength (Strasser et al., 2013), thus the ultrasound scan of VLO will indirectly establish if the exercise programme has increased in maximum voluntary contraction.

The method of scanning the VLO is explained below:

2.12.3.1 Fascicle length & Pinnation Angle

1. Position the participant supine on the examining couch with the leg as straight as possible.

2. Locate the greater trochanter and measure along the thigh to the mid patella. Mark on the thigh 50% of this length.

3. Place the probe at 50% thigh length. Moving the probe along the medio-lateral axial axis, identify the medial border (MB) and lateral border (LB) of the VLO muscle.

4. Measure the length between MB and LB. Calculate half of this distance and mark position on the skin. This position corresponds to the mid axial point at mid-sagittal length.

5. Position the probe sagittally along this line and with the mid-point of the probe aligned with the mid axial point. Acquire three images.

6. Each ultrasound image should show clear superficial and deep aponeuroses and entire fibre fascicles. Your top priority is to adjust the probe position (making very small rotation movements of the probe) so as to track the entire length of fascicles.

If the probe is not positioned parallel to the fascicles, some fibre fascicles cannot be tracked from one insertion (on the superficial aponeurosis) to the next (on the deep aponeurosis).

2.12.3.2 Muscle Volume

1. From the thigh length, mark on the skin the position corresponding to 70%, 60%, 50%, 40%, 30%, and 20% (proximal to distal).

2. Select VPan mode (panoramic view) on the ultrasound (select tools, then VPan). Move the probe along the medio-lateral axial axis from the medial border (MB) to the lateral border (LB) of the vastus lateralis muscle, taking a VPan image at each thigh length.

2.12.3.3 Image analysis

Images are transferred to a PC for post-analysis using Image J (available as free software online).

1. Fascicle length & Pennation Angle: Calibrate the image using the scale provided for each of the three images acquired. Draw a line along the upper and lower aponeurosis. Measure 3 fascicles along the image from the upper to lower aponeurosis. Take the fascicle length and also the fascicle angle.

2. Muscle thickness can also be measured on the image at the distal edge, 50% and the proximal edge by measuring from the upper to the deep aponeurosis.

2.12.4 Maximum Voluntary Contraction (MVC) - Isokinetic Contraction of Quadriceps and Hamstring Muscles

Isokinetic contraction of quadriceps and hamstring muscles was assessed using Computer Sports Medicine, Inc (CSMI) HUMAC / NORM Testing and Rehabilitation System (Model 770). The isokinetic strength of quadriceps and hamstring muscles at 60 degrees/second and 180 degrees/second were assessed to establish if exercises intervention improved the dynamic strength of knee extensors and flexors, respectively. Quadriceps muscles strength deficits are associated with knee OA (Palmieri-Smith et al., 2010, Hurley, 2003). The standardised protocol utilised in the previous studies (Tan et al., 1995b, Tan et al., 1995a) was used for this study. It is deemed a valid and reliable assessment method (Lienhard et al., 2013) to assess the strength of knee extensors and flexors.

Each participant performed three repetitions of maximal voluntary isokinetic knee extensions and flexion with the affected leg on baseline and post-intervention sessions. Isokinetic torque was measured in the seated position on a Computer Sports Medicine, Inc (CSMI) HUMAC / NORM Testing and Rehabilitation System (Model 770) isokinetic dynamometer at 60 and 180° / second angular velocities. There was 30 seconds rest between each testing and one minute break between 60 and 180° / second angular velocities.

The maximum torque limit was set at 300 N.m, and the sampling frequency was set to 200 Hz.

In order to have consistent maximum voluntary isokinetic peak torque, these standard principles were used in this study (Gandevia, 2001).

1- All maximal efforts should be accompanied by some instruction and practice.

2- Performance feedback should be given during the efforts (e.g., clear visual display) rather than delayed until after.

3- Appropriate standardised verbal encouragement should be given, preferably by the investigators, rather than an audiotape.

4- Subjects must be allowed to reject efforts that they do not regard as “maximal,” although with care, this occurs rarely.

5- In studies that involve repeated testing within a session, additional precautions are needed. The gain of any real-time visual feedback should be varied so that the subject is not necessarily aware of the magnitude of any decline in performance; the aim is to maximise performance without necessarily providing a calibrated indicator of it.

Each participant was placed in an upright seated position and secured to both the dynamometer and corresponding chair to the manufacturer specifications to eliminate extraneous movements and maintain a constant hip joint angle (90°). All participants were positioned as described by (Goslin and BR, 1979). These principles involved a parallel alignment of the limb with the lever arm of the dynamometer, which, in turn, was aligned with the anatomical axis of rotation of the knee joint (Lateral femoral condyle), and proper stabilisation, in order to prevent any other movement that could affect the measurements.

The resistance pad was placed approximately at the ankle joint, and the subject would be strapped at its thigh, waist and chest. All strength repetitions were performed with the arms folded across the subject's chest and emergency stopper in their hand.

In order to accomplish maximum values, each subject was allowed to look at the computer screen for visual feedback and received constant verbal encouragement to perform better on each test repetition. Furthermore, the subjects were instructed to work as hard as possible in the direction of the movement. The best peak torque of the three test contractions was recorded for data analysis at each angular velocity. Torque values from the trials were recorded in newton meter (N.m).

2.12.5 Physical functions (Time up and go test, 30-second sit to stand test)

The 30-second sit to stand test (30CST) and the 'timed up and go' (TUAG) test were used to see if participants improved their functions. 30CST has shown excellent reliability and validity (Gill and McBurney, 2008, Gill et al., 2012, Jones et al., 1999). TUAG has been widely used in clinical setups and is a valid tool to assess necessary functional mobility (Bennell et al., 2011, French et al., 2011, Halket et al., 2010, Kennedy et al., 2006, Mizner et al., 2011, Podsiadlo and Richardson, 1991, Zeni et al., 2010).

For 30CST, intraclass correlation (ICC) ranged from 0.93 (95% CI 0.87-0.96) to 0.98 (95% CI 0.96-0.99), established inter-rater reliability between two

administrations of the same test by two different raters on the same day and this reliability was assessed at three-time points over 15 weeks in 42 patients awaiting total hip or knee replacement (Gill and McBurney, 2008). This value ranged from 0.97 (95% CI 0.94-0.98) to 0.98 (95% CI 0.97-0.99) when done by the same rater. A similar group of authors reported excellent construct validity and correlation to WOMAC with ICC = -0.62 (95% CI -0.74 to -0.47) (Gill et al., 2012) in osteoarthritis sufferers. They reported responsiveness as standardized response mean (SRM) = 0.84 (95% CI 0.61-1.07).

TUAG test has shown excellent test/retest reliability (ICC=0.75) (Dobson, 2015) and inter-rater reliability (ICC=0.87; 95% CI= 0.74-0.94) (Wright et al., 2011) in patients with osteoarthritis of hip and knee. A relatively new study (n=60, aged 45-70 with knee OA) reported excellent intra- and inter-rater reliability (ICC .97 and .96, respectively) (Alghadir et al., 2015). The standard error of measurement (SEM) values were 0.17 seconds and 0.16 seconds, based on repeated measurements for inter- and intra-rater, respectively. It is the speculative difference between an observed score on any specific assessment and the actual score for the method (Association, 2018).

30CST and TUAG are standardised tests and performed according to a routine protocol. 30CST involved recording the number of stands a person could complete in 30 seconds. It was administered using a folding chair without arms, with a seat height of 17 inches (43.2 cm). The chair, with rubber tips on the legs, was placed against a wall to prevent it from moving.

The participants were seated in the middle of the chair, back straight; feet approximately shoulder-width apart and placed on the floor at an angle slightly

back from the knees, with one foot slightly in front of the other to help maintain balance. Arms were crossed at the wrists and held against the chest.

The task was demonstrated to participants both slowly and quickly. This is done so that those participants who were slow could follow the process and understand it. The same reasoning applied for demonstrating it quickly to the participants who were fast paced. It was also explained to participants that they had to touch their buttocks to the chair when descending, and their knees should fully extend when ascending from the chair for it to be counted as repetition, more applicable to fast-paced participants.

The participants were allowed to practice a repetition or two before completing the test.

If a participant used their arms to complete the test, they were scored 0.

The participants were encouraged to complete as many full stands as possible within 30 seconds and instructed to sit between each stand fully.

The score was counted as the total number of stands within 30 seconds (more than halfway up at the end of 30 seconds counts as a full stand). Incorrectly executed stands were not counted.

TUAG was done according to standard protocol. The procedure was explained to the participants, and a practice trial was completed before the timed trial. The participant started in a seated position. The participant would stand up upon the assessor’s command, walk 3 meters, turn around, walk back to the chair, and sit down. The time was stopped when the participant was seated. The participants could use an assistive device, if needed. If the assistive device was used, it was documented.

2.12.6 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

I used the WOMAC score, which is widely utilised in the evaluation of hip and knee osteoarthritis. It is a self-administered questionnaire made of 24 items and consists of three subscales covering pain, stiffness, and physical function. Three subscale scores range from 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function, making the overall range from 0-96. I used a 5-point Likert based version of WOMAC. A higher score on the WOMAC indicates worse pain, stiffness, and functional impairments. It has been used extensively and deemed a valid and reliable tool (Bellamy et al., 1988, McConnell et al., 2001, Gill et al., 2012, Collins et al., 2011).

A systematic review evaluated 37 outcome measures used in 47 studies conducted on musculoskeletal conditions of the knee joint and reported only ten outcome measures were supported with sufficient quality and breadth of evidence to demonstrate ‘truth’ and ‘discrimination’ (Howe et al., 2012). Out of these ten outcome measures, only WOMAC was specific for knee OA whereas other outcome measures were tailored for other knee conditions such as Lysholm and Tegner (two different outcome measures) for ligament injuries, Western Ontario Meniscal Evaluation Tool (WOMET) for meniscal injuries, Anterior Knee Pain Scale (AKPS) for patellofemoral pain, goniometer measurement for assessing the range of motion, American Academy of Orthopaedic Surgeons (AAOS), Knee injury and Osteoarthritis Outcome Score (KOOS), The International Knee Documentation Committee subjective knee

form (IKDC) for a wide range of knee conditions and Lower Extremity Functional Scale (LEFS) for lower limb general conditions. As WOMAC is outcome specific to knee OA, it was one of the reasons I used it in our study.

Gandek B. (2015) conducted a systematic review that summarised the measurement properties of the WOMAC using data from 76 articles in 22 countries and reported that WOMAC pain, function, and stiffness symptom scales consistently met accepted reliability standards for group-level comparisons (Gandek, 2015). Across all studies combined, the median Cronbach's coefficient alpha was >0.70 for the pain and stiffness scales (minimum level recommended for group analyses) and 0.95 for the function scale (minimum level recommended for individual analyses) (Hays and Revicki, 2005). Median test-retest reliability statistics were highest for the function scale but generally were 0.70 for all three scales. Intraclass correlation coefficient (ICC) ≥0.7 is considered acceptable for test-retest reliability (Fayers and Machin, 2013). Gandek B. (2015) reported that across 12 studies that published correlations among all 3 WOMAC scales, the median correlation was r = 0.81 (range 0.68–0.86) between the WOMAC pain and function scales, r = 0.64 (range 0.39–0.73) between the pain and stiffness scales, and r = 0.68 (range 0.42–0.78) between the function and stiffness scales. Correlation coefficient (Pearson’s r) of >0.50, 0.35–0.50, and <0.35 were considered strong, moderate, and weak, respectively (Juniper, 1996).

One of the limitations of WOMAC is that the WOMAC pain scale is considered as a measure of pain during physical functioning rather than a distinct measure of pain (Gandek, 2015). This has been reported by another systematic review evaluating the physical function sub-scale of WOMAC and reported that

respondents technically only reported the extent of functional limitation attributed to pain, discomfort or arthritis, which might not reflect their total limitation (White and Master, 2016). Another review included 62 trials using WOMAC in the cohorts of hip and knee OA and concluded that details on the use and scoring of the WOMAC were often not reported (Copsey et al., 2019). They recommend that trials should report the version of the WOMAC and the score range used.

2.12.7 General health questionnaire (MSK- HQ)

For quality of life, stiffness, generalised well-being, difficulty with sleeping and understanding of the diagnosis and treatment, I used patient-reported outcome measure MSK-HQ. This instrument covers a broad aspect of musculoskeletal conditions, and I used it in our study as per recommendations of versus arthritis. The questionnaire consist of 14 questions and all of these questions are summed together (response coded from ‘not at all’ = 4 to ‘extremely’ = 0, except for question 12 and 13 which are coded in the reverse order) providing a total score from 0-56, with higher score indicating better MSK health. Recent studies have shown it to be reliable and valid (Hill et al., 2016b, Hill et al., 2016a). It enables clinicians and participants to monitor progress over time and response to treatment. Considering individual components of score, such as generalised wellbeing or quality of life, can assist the clinician in establishing the deficiency in the participant’s health; therefore, treatment or management can be targeted holistically toward those deficiencies.

2.12.8 Sleep Assessment using Actigraphy

Actigraphy is a method that records and incorporates the occurrence and intensity of limb movement activity over time (Fekedulegn et al., 2020, Smith et al., 2018). Actigraphy devices can be worn on the wrist, ankle, or waist over days to weeks. For sleep applications, the devices are typically worn on the wrist or ankle. Although polysomnography (PSG) is considered the gold standard for assessing sleep, actigraphy is more convenient, less invasive, and lower cost than PSG (Fekedulegn et al., 2020, Smith et al., 2018). Additionally, collecting actigraphy data over multiple nights in the participant's own environment can provide more reliable estimates of sleep than PSG, which is typically performed in a sleep laboratory (Rupp and Balkin, 2011, Blackwell et al., 2008). Actigraphy has been validated against PSG in multiple populations (Smith et al., 2018, Van De Water et al., 2011, Rupp and Balkin, 2011). The estimated agreement between PSG and actigraphy ranged from 91 to 93% in the previous comprehensive review (Ancoli-Israel et al., 2003). A recent meta-analysis of 15 studies compared actigraphy to PSG for the assessment of total sleep time (TST) in patients with suspected or diagnosed insomnia and a clinically significant range of possible mean differences of 35.12 minutes (95% CI: 8.07 to 27.05) with an overall mean difference of 10.14 minutes (Smith et al., 2018). The same study conducted a meta-analysis of 12 studies comparing actigraphy to PSG to assess onset latency and a clinically significant range of possible mean differences of 6.78 minutes (95% CI: 2.29 to 9.07) with a mean difference of 6.17 minutes. Similar findings were observed for wakefulness occurring after defined sleep onset (WASO), and a meta-analysis of 12 studies showed a clinically insignificant range of possible mean differences of 33.22

minutes (95% CI: 13.68 to 19.54), with a mean difference of 1.5 minutes. These ranges for TST, onset latency and WASO are narrow enough that actigraphy can be reliably used to provide an objective assessment of these sleep parameters for the purpose of making clinical care decisions (Smith et al., 2018). They also reported a meta-analysis of 9 studies comparing actigraphy to PSG for the assessment of sleep efficiency (SE) and reported a clinically insignificant range of possible mean differences of 7.8% (95% CI: 4.9% to 3.0%), with a mean difference of 1%. This large range indicates actigraphy cannot be reliably used to provide an objective assessment of SE that is comparable with PSG. They concluded that there is sufficient evidence of validity and utility of actigraphy in assessing sleep continuity in conjunction with sleep logs and PSG (Smith et al., 2018).

All participants were given an actigraphy device that was CE marked and called ActTrust. It has 3 axis, 12 bits accelerometer with a sampling rate set to 25Hz. They were advised to wear it regularly except if there were going to swim. The actigraphy device was collected and data was pulled from the device and added to the database on a follow-up session.

The actigraphy device monitored:

2.12.8.1 Time in bed (TIB):

As name indicates, this is the total time spent in the bed by a participant which sleep monitory equipment is worn and activated. This is an important factor as a participant who only spends three to four hours in bed cannot reasonably go through all normal stages and cycles of sleep.

2.12.8.2 Total Sleep Time (TST):

It is the total amount of sleep time scored. This is recorded as a time from sleep onset to sleep offset and described in minutes.

2.12.8.3 Onset Latency or Sleep Latency (SL):

This is defined as the duration of time between when the lights are turned off as the participant attempts to sleep until the time participant actually falls asleep and recorded in minutes.

2.12.8.4 Wakefulness occurring after defined sleep onset (WASO):

It is defined as periods of wakefulness occurring after defined sleep onset and reflection of sleep fragmentation.

2.12.8.5 Sleep efficiency (SE):

This refers to the percentage of total time in bed actually spent in sleep. The total amount gives a general estimation of the overall quality of sleep.

2.12.9 Pittsburgh Sleep Quality Index (PSQI)

In addition to actigraphy, I used the Pittsburgh sleep quality index (PSQI), which has been used in multiple studies and validated to measure sleep disturbances (Backhaus et al., 2002, Carpenter and Andrykowski, 1998, Buysse et al., 1991, Finan et al., 2013a, Taibi and Vitiello, 2011). Previous studies compared PSQI and parameters from actigraphy data, including older cohort (Beaudreau et al., 2012, Spira et al., 2011) and non-clinical samples (Grandner et al., 2006) reported a weak correlation coefficient between PSQI

and actigraphy data. The purpose of adding the PSQI questionnaire was to assess if I could see any improvement in subjective sleeping reported by participants post-exercise intervention.

A systematic review and meta-analysis reviewed 37 studies based on sleep dysfunction in clinical and non-clinical samples. They reported that nine studies contained Cronbach's alpha coefficients greater than or equal to 0.70 (Mollayeva et al., 2016). They also noted that two studies reported ICC ≥0.70, the first one reporting intraclass correlation coefficient (ICC) of 0.86 (Buysse et al., 1989) and the second study denoting ICC of 0.81 (Knutson et al., 2006). The test period for the first study was two weeks and one year for the second study between test-retest. Mollayeva et al. (2016) reported a strong association between the PSQI total score and the insomnia severity index (ISI) total score (r = 0.80) (Morin et al., 2011), sleep problems from symptom experience reports (r = 0.72–0.77) (Carpenter and Andrykowski, 1998), sleep restlessness score (r = 0.72–0.77) (Carpenter and Andrykowski, 1998), and sleep efficiency score from the sleep diary (r = −0.76) (Grandner et al., 2006). Weak to moderate associations were reported between the PSQI global score and polysomnography (PSG) sleep maintenance (Spearman's rank correlation coefficient [ρ]= −0.33), sleep efficiency (ρ = −0.34), and microarousal index in younger (ρ = 0.39), but not in older healthy subjects polysomnography (Buysse et al., 1991). PSQI showed a strong correlation with related sleep constructs (Mollayeva et al., 2016, Morin et al., 2006, Nicassio et al., 2014) and poor correlation with unrelated constructs (Bush et al., 2012). Mollayeva et al. (2016) concluded that the best evidence synthesis for the PSQI showed strong reliability and validity and moderate structural validity in various samples,

suggesting the tool fulfils its intended utility. The PSQI suffers from the same challenges as other self-report inventories in that scores can be easily overstated or understated by the person completing them.

2.12.10 Body Mass Index and bioimpedance analysis

The bioimpedance unit assessed the body mass index (BMI) of the participants. The procedure included:

1. Explanation to the subject what was going to be done by the assessor. The participant was given an adequate explanation of the experimental protocol to ensure that an 'informed' consent to participate was given.

2. The participant was advised to lie supine on a couch/bed, with legs slightly apart and arms away from the body. The health and safety of the participant was of primary concern during the experiment.

3. Two electrodes were placed on the back of the hand. See diagram 2-1.

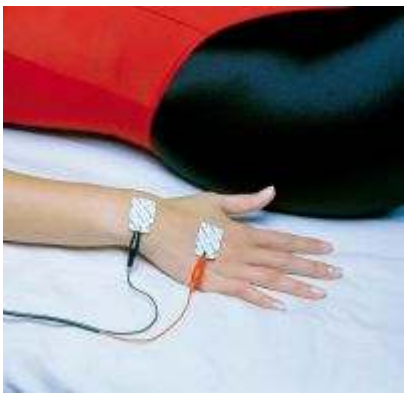


Figure 2-3: Attachment of bioimpedance electrodes on hand.

4. Two electrodes were placed on the upper aspect of the foot (on the corresponding side). See diagram 2-2.

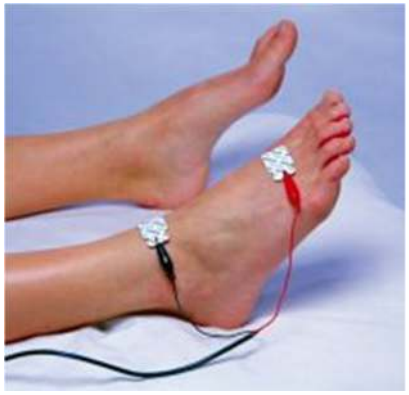


Figure 2-4: Attachment of bioimpedance electrodes on foot.

5. The leads were attached so that the red electrode was always the one at the extremity (The distal electrode on both the hand & foot).

6. The machine was turned on using the switch on the side.

7. ‘Test Number’ was displayed by the device, and it was documented. After that, 'Enter' was pressed to proceed.

8. The participant’s demographics were entered into the device. (These include sex, age, height, weight, hip and waist circumferences, and physical activity levels).

9. Once all information had been inputted into the Analyser, the participant was instructed to stay very still. After rechecking the electrodes and leads, ‘Enter’ was pressed to start the analysis.

10. When completed, the assessor recorded the values onto paperwork, and it was shifted to database later.

2.13 Sample Size and Justification

A recent systematic review of 44 high-quality exercise trials for knee OA pain (3537 participants) (Fransen et al., 2015) found an average effect of 12/100 VAS points corresponding to 0.49 standard deviations. Based on this estimated effect size, a sample size of n=60 per group was needed to achieve 75% power, with an alpha level set to 0.05. The estimated dropout rate for exercise interventions is 11-12% (Coleman et al., 1999); therefore, a sample of 67 per arm was planned (corresponds to 80% power).

2.14 Randomisation and Blinding

Participants were randomised by a research team at Academic Rheumatology using the https://sealedenvelope.com/ software. Generation of a randomisation schedule included obtaining the random numbers and assigning random numbers to each subject. This software was used for generating a randomisation schedule included obtaining the random numbers and assigning random numbers to each subject. The block randomisation feature enabled by this package was used to allow predictability in the requirement for tablets for the treatment arm (see section 2.9). The code break was kept online, and the research manager was responsible for keeping track of it.

As per the cohort multiple randomised controlled trial design mentioned by another study (Moseley et al., 2002), individuals were assessed to establish their suitability for this study. Once they were deemed eligible for the study, they were randomised to the control and interventional groups. At this stage,

individuals knew that they belong to one group or the other and hence blinding was not possible. Because the lack of masking might affect the motivation of participants randomised into the control arm, individuals in the control arm were offered access to the web-based exercise programme after six weeks, if they wished to use it to avoid a nocebo effect in this group. Blinding such interventional studies are difficult to achieve as participants will know their treatment, and unfortunately, blinding assessors was not practical for this study. Although the research team liaised with the participants to inform them whether they were in the control group or the intervention group, however during the assessments, some participants shared this information with the assessor. And hence blinding of assessor was not possible.

2.15 Monitoring of Adherence

The JA intervention encouraged participants to exercise daily by sending daily e-mails. These e-mails served the purpose of reminding these participants to exercise daily.

Compliance was assessed and collected by the JA app and based on the participants completing their allocated exercises and educational sessions. These exercises and educational sessions were interactive and encouraged participants to finish their tasks (exercises or educational sessions) and press ‘next’ after each set of exercise/educational videos until the whole session was over. This was transcribed as a ‘completed’ session on the portal of the physiotherapist. Any partially completed session was marked as a not completed session.

Additionally, SG was able to monitor the adherence of participants by logging in to the physiotherapy portal. This portal served as a platform to interact with the participants via chat, and it allowed SG to manually monitor participants' adherence. This adherence data were available for all the active participants for that week; however, the system did not allow SG to save or capture this data. This online portal had no in-built facility to prompt or define non-adherence, and therefore adherence was monitored manually by SG using the online portal. SG interacted with those participants who did not exercise for four consecutive days and tried to establish whether they were having issues with pain management or other problems with their personal life or dropped out of this study. This will be discussed in section 3.12, ‘Results for adherence’ and section 6.11, ‘adverse events and section 6.12 ‘adherence’.

2.16 Data Management

In this trial, outcome data were collected during the first session and the last session. Additionally, actigraphy collected the sleeping pattern. Data collection from the face to face visits and actigraphy was collated by trained local research staff, and data entry in a relational MS Access database was completed in a standardised fashion. The clinical research forms (CRF) from the first and last visit were sent to the data entry site. A central data manager performed and monitored data entries. This included questionnaires (MSK-HQ, PSQI, WOMAC) and data from QST, 30CST, TUAG, and MSK-USS.

Entries on study forms were verified by inspection against the source data. The data manager regularly checked a sample of the forms (10%) to verify all

entries made. Also, the subsequent capture of the data on the study database were checked by the same data manager. Where corrections were required, a full audit trail and justification was carried out.

2.17 Statistical Analysis Plan

The statistical analysis plan (SAP) was written as a part of the protocol for this study. The SAP has been added here, so that intention to calculate results is clear.

2.17.1 Statistical Principles

Alpha level was set to 0.05. 95% confidence intervals will be presented (if data allows for parametric analyses).

Adjustments for multiple testing were not performed as there was only one primary outcome for which the study was powered. Adjustment for multiple secondary outcomes would have resulted in a decrease of statistical power for the key purpose of the study. Analyses on other outcomes should be considered exploratory and interpreted in light of the general pattern of effects rather than solely based on individual p-values.

Adherence to the JA intervention was defined as the percentage of the sessions completed.

Analyses were planned to be based on the Intention to treat (ITT) population; however, because I had to stop the study due to COVID-19 lockdown in March

2020, I performed per-protocol analysis as 27 participants (14 in control and 13 in intervention arm) enrolled into the study were not able to attend the follow-up visit. The implications of this are discussed in chapter 6.

Since there were no risks associated with the JA intervention, safety analyses were not performed. Any harm or adverse events are reported in the thesis (section 6.11; Adverse Events) and will be published in any forthcoming publications.

2.17.2 Interim Analyses and stopping guidance

No interim analysis was planned or performed. As there were no significant adverse events expected, there was no provision to stop the trial early.

2.17.3 Intended Analysis Plan

The distribution for each difference score will be evaluated. If the score follows an approximately normal distribution with no apparent outliers, between-group differences will be analysed through independent t-test or ANOVA. If baseline demographic variables (age, gender, BMI and K/L) differ between the groups despite randomisation, those variables, as well as baseline scores for the outcome variable, will be calculated/included in the ANOVA model to check for potential confounding effects. The confounding effect will be evaluated through "change in estimate" (Mickey and Greenland, 1989), meaning that the variables will be kept in the model if the inclusion affects the between-group results with >15%. Within-group differences will be analysed through paired samples t-test.

If the difference scores clearly deviate from a normal/symmetric distribution, the comparisons will instead be performed through non-parametric analyses. For the between-group comparisons, the Mann-Whitney test will be applied and for the within-group comparison, Wilcoxon signed rank test will be used. Results will be presented as median scores (IQR) and P-values.

2.17.4 Intended missing data calculation

I planned to use the multiple imputations (MI) methods if missing data are >5% (Jakobsen et al., 2017); however, if missing data <5%, then I will use the group mean imputation method. Based on the missing data (primary outcome or secondary outcome, baseline values or follow-up values), the intention was to assess which type of MI was required, single value regression analysis, monotonic imputation or the Markov chain Monte Carlo (MCMC) method (Jakobsen et al., 2017). This intended plan was subject to the appropriateness of MI method for missing data according to the conditions described by Jakobsen et al. (2017) and shown below in Figure 2-5.

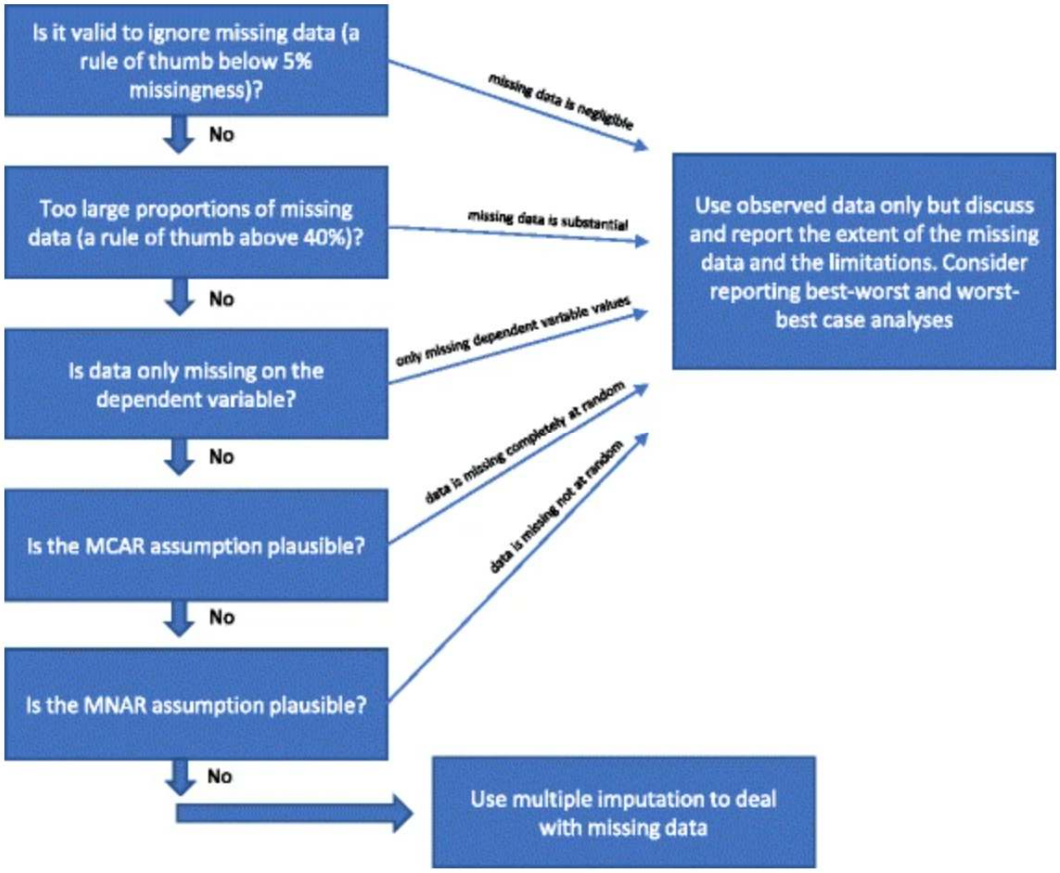


Figure 2-5: Flowchart explaining when multiple imputations should be used to handle missing data when analysing results of randomised clinical trials. Abbreviations: MCAR, Missing completely at random; MNAR, Missing not at random (Jakobsen et al., 2017).

2.18 Statistical Analysis

The missing data values were imputed using the mean imputation method as missing data was <5%. The frequency of missing values is shown in Appendix 3. Baseline and follow up scores were presented for each group as means and standard deviations (SD). For all outcome variables, a difference-score between baseline and follow up was calculated and used as outcome variables in the comparisons between groups.

2.18.1 Analysis of Intra and Inter-Observer reliability

Intra-observer reliability was examined whereby measures from the first day (SG) were compared to the second day (SG) measures.

Inter-observer reliability was examined whereby measures from a given day (SG) were compared to measures from the same day (GF for x-rays and DM for QST).

As K/L scoring is an ordinal scale (Sheehy et al., 2015), therefore Weighted Kappa was used to examine the agreement for the K/L scoring system. The strength of agreement was classified according to criteria in Table 2-1 (Landis and Koch, 1977).

Value of Kappa	Strength of agreement
0 - 0.2	Slight
0.21 - 0.4	Fair
0.41 - 0.6	Moderate
0.61 - 0.8	Substantial
0.81 - 1	Almost Perfect

Table 2-1 Strength of agreement for the value of kappa

Intra-class correlation co-efficient (ICC) was reported for QST. Criteria for describing the strength of ICC reliability indices have been defined as less than 0.5 indicates poor reliability, between 0.5 - 0.75 moderate reliability, between

0.75 - 0.90 good reliability and > to 0.90 excellent (Portney and Watkins, 2009). The results of Intra- and inter-observer reliability are given in section 3.6.

2.18.2 Primary Analysis

The primary comparison between groups was performed using a two-sided t-test for the mean difference in NRS at follow-up versus NRS at baseline (primary outcome). The difference within arms between baseline and follow-up was assessed using a paired t-test as secondary analysis.

2.18.3 Secondary Analysis

A similar model was used for other variables (QST, isokinetic strength of quadriceps and hamstrings, WOMAC, MSK-HQ, PSQI, 30CST, TUAG, and MSK-USS). Further analysis of sub-components of WOMAC and PSQI was also carried out using a two-sided t-test to see a statistically significant difference. The actigraphy data and histograms of different sleep variables did not display bell-shaped distribution (Appendix 4). Therefore, the comparisons between groups were made using spearman's correlation and Mann-Whitney two-sided tests. This is discussed further in Chapter 4.

2.18.4 Analysis for Other variables

Age, BMI, sex, medication for knee OA and KL scores at baseline were assessed for both arms of the RCT.

Additionally, the adherence rate was calculated as the percentage of online sessions attended by the intervention group.

2.18.5 Statistical Software

The data were analysed using StatsDirect V3.2.10, SigmaXL 8.15 and SPSS v26 by the author (SG).

Chapter 3 Results

3.1 Background

Knee OA is a common form of arthritis globally (Felson, 1996, Neogi and Zhang, 2013, Reynaud et al., 2020). The rate of knee arthritis is as high as that of cardiac disease and is the most common problem in individuals over 65 (Guccione et al., 1994). This study explores the benefits of internet-based exercises in patients with knee OA to establish if their pain decreases after six weeks. The main focus of this chapter will be on pain, muscle strength and ultrasound.

3.2 Flow Chart

The recruitment started in Oct 2018, whereas the trial begun in Nov 2018. Recruitment and trial were stopped in March 2020 due to COVID-19 Pandemic.

The flow chart is shown in Figure 3-1.

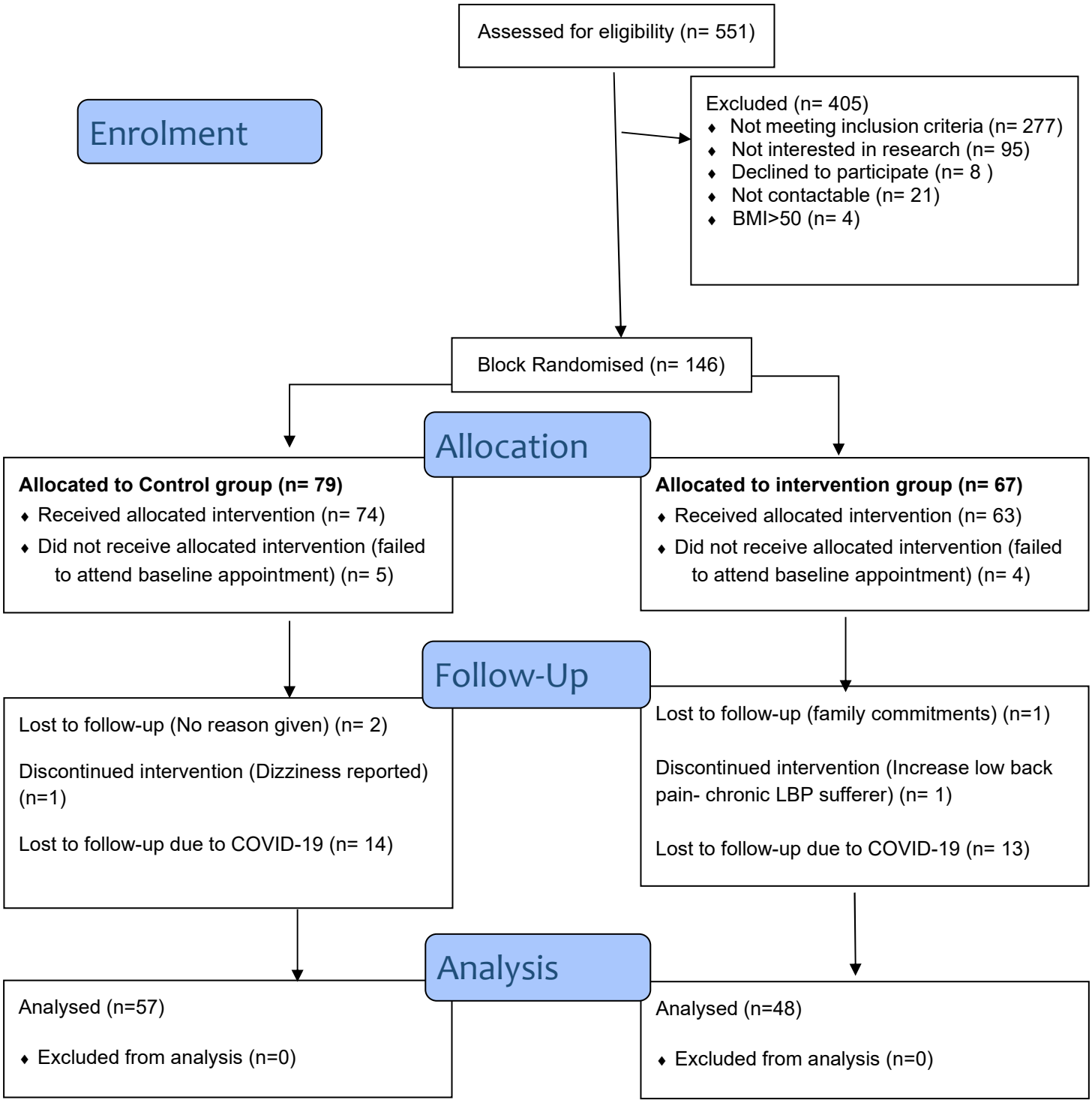


Figure 3-1: Flow chart for iBEAT-OA Randomised Controlled Trial

3.3 Distribution of the data

The distribution of the data was assessed and deemed to be bell-shaped and quantitative. This was established by plotting histograms (Mishra et al., 2019, Thode, 2002). Most histograms displayed bell-shaped distribution, and histograms are shown in Appendix 4. Under the central limit theorem, the sampling distribution will be normal if the sample is large enough. Given the sample size included (n=104) and the bell-shaped distributions observed, parametric methods were chosen for analysis.

The only exception was actigraphy data, and histograms of different sleep variables extracted from actigraphy did not display bell-shaped distribution (Appendix 4); therefore, non-parametric methods were chosen for analyses of actigraphy data.

The baseline demographics between both groups have been elaborated in section 3.7, 'Demographics of participants'.

3.4 Missing Data Imputation

No data was missed for the primary outcome measure (NRS). There were five values missed for WOMAC (Three values for control group at baseline, one value for control group at follow up and one value for intervention group at follow up) and five values for MSK-HQ (one value for control group at baseline, one value for intervention arm at follow up, two values for intervention group at baseline and one value for intervention group at follow-up). Additionally, three

values for PSQI were missed (two values for the control group at follow-up and one for the intervention group at baseline). The missing values are shown in Appendix 3. As these values are minuscule (<5%), these missing values were calculated by group mean imputation.

3.5 Recruitment Issues and Dropouts

Figure 3-1 shows recruitment issues that this study had. The vast majority of interested participants were ruled out due to not meeting inclusion criteria. Due to COVID-19 lockdown in the UK (March 2020), the study was ended before 27 participants (14 in control and 13 in intervention arm) had a chance to complete face-to-face follow-up. In addition, three participants in the control group and two participants in the intervention group were lost to follow-up. Two dropouts in the intervention group provided reasoning to leave this study. One participant in the intervention group reported increased family commitments and therefore was unable to continue. Another participant reported increased low back pain, which is discussed further under section 6.12, “adverse events” in chapter six. Two out of three dropouts in the control group did not give reason, and one participant reported a blood pressure drop after the baseline visit. This is discussed further in the adverse events section 6.12.

3.6 Results of Analysis of Intra and Inter-Observer

Following earlier introduction of this analysis in section 2.17.1, twenty participants with mean age 69.5 years (range 55-76), 12 females and eight

males, had their knees x-rays reviewed twice by the same examiner (SG) within five days (Intra-observer reliability). These x-rays were reviewed by another senior research fellow (GF) on the same day to establish inter-observer reliability.

Kappa co-efficient for intra- and inter-observer agreement for the dichotomous presence or absence of radiographic features and weighted kappa values for K/L score are shown in Table 3-1.

	Kappa	
Radiographic X-rays Features	**Intra-observer**	**Inter-observer**
Osteophytes	1 p<0.001	0.92 p<0.001
Joint Space Narrowing (JSN)	0.87 p<0.01	0.82 p<0.01
Sclerosis	0.85 p<0.001	0.68 p<0.01
K/L Grading (Weighted)		
K/L	0.93 p<0.001	0.86 p<0.001

Table 3-1: Intra and Inter-observer agreement for the presence of radiological features of x-rays and K/L grading

The level of agreement for osteophytes, joint space narrowing, and sclerosis was almost perfect, and for sclerosis was substantial for inter-observer reliability. Similarly, the intra and inter-observer level of agreement for KL grading was almost perfect.

For QST, 15 participants with a mean age of 65.3 (range 56-73), nine females and six males, had their most painful knee assessed by the assessor (SG) and a research colleague (DF). Furthermore, for intra-observer reliability, SG assessed five knees of healthy volunteers (mean age of 37 [range 22-43], two females and three males) on two separate days within five days. The ICC

values demonstrate that the reliability for both intra- and inter-observer measures were good to excellent for QST methods show in Table 3-2.

	ICC (95% CI)	
QST	**Intra-observer**	**Inter-observer**
Pressure Pain Threshold (PPT)	0.87 (0.81-0.93)	0.81 (0.7-0.91)
Temporal Summation (TS)	0.94 (0.9-0.97)	0.84 (0.74-0.93)
Conditional Pain Modulation (CPM)	0.84 (0.8-0.89)	0.79 (0.68-0.9)

Table 3-2: Intra-class correlation coefficients (ICC) and 95% confidence interval (CI) for reliability of QST.

3.7 Demographics of Study Participants

The baseline characteristics (Age and BMI) between the treatment and control arms were assessed by two-tailed t-tests; no difference for these characteristics was found between both arms. Chi-square tests evaluated sex and KL characteristics between the treatment and control arm, and again no statistically significant difference between both arms was observed (Table 3-3).

The mean baseline demographics were similar for participants in the two groups, as shown in Table 3-3, except for the PSQI sleep questionnaire scores, and this difference is discussed in chapter 4. The mean baseline demographic in the excluded 17 participants in the control group (14 due to COVID-19 and 3 dropouts) and the 15 participants in the intervention group (13 due to COVID-19 and 2 dropouts) were similar to the participants included in the respective group (Table 3-3).

Characteristic		Control Group (n=57)	Intervention Group (n=48)	P- values (b/w group differences at baseline)	Excluded Control Group (n=17)	Excluded Intervention Group (n=15)
Age (year) Mean (SD)		68.0 (8.6)	65.2 (9.7)	P= 0.13	64 (8)	64 (5)
Women / Men (%)		37 (64.9%) / 20 (35.1%)	34 (70.8%) / 14 (29.2%)	P= 0.52	11 (64.7%) / 6 (35.3%)	11 (73.3%) / 4 (26.7%)
BMI		31.9 (5.9)	30.4 (5.5)	P= 0.19	28.7 (4.6)	30.5 (4.9)
Radiographic Score (K/L)		2.1 (0.96)	2.0 (1.0)	P= 0.64	1.9 (0.8)	1.9 (0.9)
1		18 (31.6%)	19 (39.6%)	NA	6 (35.3%)	5 (33.3%)
2		22 (38.6%)	13 (27.1%)	NA	8 (47.1%)	7 (46.7%)
3		11 (19.3%)	11 (22.9%)	NA	2 (11.8%)	2 (13.3%)
4		6 (10.5%)	5 (10.4%)	NA	1 (5.9%)	1 (6.7%)
	Sub scores	Mean (SD)	Mean (SD)	P-values	Mean (SD)	Mean (SD)
NRS pain		4.7 (2.1)	4.4 (2.0)	P=0.54	4.3 (1.5)	4.3 (1.6)
WOMAC	Pain	7.8 (3.7)	8.0 (3.9)	P=0.67	NA	NA
	Stiffness	3.1 (1.6)	4.0 (1.7)	P=0.71	NA	NA
	Physical function	28.3 (12.8)	26.8 (12.9)	P=0.53	NA	NA
TUAG		9.9 (3.6)	9.0 (1.4)	P=0.59	9.1 (2.5)	9.4 (1.9)
30CST		9.2 (4.3)	9.3 (2.7)	P=0.9	10.1 (1.7)	9.8 (1.9)
MSK-HQ		28.4 (10.1)	30.7 (9.9)	P=0.25	NA	NA
PSQI		8.5 (3.7)	9.18 (3.4)	P=0.01	NA	NA
PPT	Superolateral Patella	317.3 (170.2)	314.4 (153.7)	P=0.93	350.1 (84.8)	315.6 (150.7)
	Superomedial Patella	334.1 (147.4)	326.0 (149.9)	P=0.78	370.5 (131.7)	305.4 (103.8)
	Medial Joint line	355.1 (202.5)	318.7 (159.0)	P=0.31	359.7 (173.0)	319.0 (105.4)
	Tibialis Anterior Muscle	367.0 (182.4)	386.40 (175.8)	P=0.58	372.8 (150.2)	373.0 (122.8)
TS		1.8 (1.8)	2.30 (1.8)	P=0.15	1.9 (1.1)	2.2 (1.7)
CPM		52.8 (110.7)	53.4 (97.6)	P=0.98	41.0 (130.4)	77.5 (100.5)
Isokinetic Strength	Q60	69.4 (42.7)	79.52 (45.6)	P=0.24	77.7 (29.8)	80.1 (37.7)
	H60	52.19 (26.7)	54.44 (29.6)	P=0.68	60.5 (23.0)	63.3 (25.3)
	Q180	40.7 (26.1)	46.10 (28.8)	P=0.31	53.1 (24.0)	49.7 (22.1)
	H180	37.3 (21.2)	40.8 (22.5)	P=0.41	47.9 (13.3)	45.2 (14.2)
Sleep Traits		**Median (IQR)**	**Median (IQR)**	**P-Values**	**Median (IQR)**	**Median (IQR)**
	Time in bed	3.57 (2.89-4.56)	3.76 (3.06-4.42)	P=0.81[a]	NA	NA
	Total Sleep Time	3.1 (2.42-3.95)	3.18 (2.63-3.82)	P=0.8[a]	NA	NA

Characteristic		Control Group (n=57)	Intervention Group (n=48)	P- values (b/w group differences at baseline)	Excluded Control Group (n=17)	Excluded Intervention Group (n=15)
Sleep Traits	Onset Latency	0.02 (0.01-0.03)	0.02 (0.01-0.03)	P=0.58[a]	NA	NA
	WASO	0.43 (0.32-0.53)	0.44 (0.34-0.59)	P=0.41[a]	NA	NA
	Sleep Efficiency	0.81 (0.7-0.86)	0.8 (0.7-0.84)	P=0.39[a]	NA	NA

Table 3-3: Baseline Demographics of iBEAT-OA RCT. Withdrawn Control Group consisted of 14 participants who did not complete RCT due to COVID-19, and three dropped out. Withdrawn Intervention Group consisted of 13 participants who did not complete the study due to COVID-19, and two dropped out. Abbreviations: 30CST, 30 second sit to stand test, counts the number of times the participant comes from a sitting position on a chair to a full standing position in 30 seconds; **BMI,** body mass index, calculated as weight in kilograms divided by height in meters squared; **CPM,** Conditioned pain modulation, ranges from 0 to maximum value measured in kilopascal (kPa); **Isokinetic Strength, Q60 & Q180,** the isokinetic peak torque of quadriceps muscles measured at 60 degrees/second and at 180 degrees/second respectively, **H60 & H180**, the isokinetic peak torque of hamstring muscles measured at 60 degrees/second and at 180 degrees/second respectively, presented in Newton meter (Nm); **K/L,** Kellgren & Lawrence score, ranging from 0-4, 0 being no OA and 4 being severe OA indicated by large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends on radiographs; **MSK-HQ,** The Musculoskeletal Health Questionnaire, 14 questions scored on a scale of 0-4 (lower scores indicate lower levels of symptoms or physical disability), the total score is the sum of all items; **NA,** Not applicable or not calculated (due to no addition into context); **NRS,** Numerical Rating Scale, 0-10 where 0 is no pain and 10 is the worst pain imaginable; **PSQI,** Pittsburgh Sleep Quality Index, ranging from 0-21, high score indicating poor sleep quality; **Sleep Traits,** Time in bed, Total sleep time, Onset latency, Wakefulness occluding after define sleep onset (WASO) and sleep efficiency, all scores showing hours, except sleep efficiency which is expressed in sleep efficiency in % divided by 100 (converted in to numbers); **PPT**, Pressure pain threshold, 0 to maximum value measured in kilopascal (kPa); **TS,** Temporal summation, ranges from 0 to 10 value on NRS; **TUAG,** Timed up and go test, measured in seconds, the participant stands up upon therapist's command, walks 3 meters, turns around, walks back to the chair and sits down**; WOMAC,** The Western Ontario and McMaster Universities Osteoarthritis Index, items are scored on a scale of 0-4 (lower scores indicate lower levels of Pain (5 items, 0-20), stiffness (2 items, 0-8), and physical function (17 items, 0-68); [a] Mann-Whitney two tailed test result.

		Control Group at baseline (n=57)	Intervention Group at baseline (n=48)	Control Group at Follow-up (n=57)	Intervention Group at Follow-up (n=48)
Outcome	Sub score	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
NRS pain		4.7 (2.1)	4.4 (2.0)	4.3 (2.08)	2.6 (2.0)
WOMAC	Pain	7.8 (3.7)	8.0 (3.9)	6.6 (3.5)	5.8 (4)
	Stiffness	3.1 (1.6)	4.0 (1.7)	3.3 (1.76)	3.2 (1.8)
	Physical function	28.3 (12.8)	26.8 (12.9)	23.9 (11.9)	19 (13)
TUAG		9.9 (3.6)	9.0 (1.4)	10.3 (4.27)	7.6 (1.49)
30CST		9.2 (4.3)	9.3 (2.7)	10.3 (4.9)	13.8 (4.6)
MSK-HQ		28.4 (10.1)	30.7 (9.9)	29.9 (10.05)	31.9 (13.9)
PSQI		8.5 (3.7)	9.18 (3.4)	7.77 (3.5)	7.91 (2.9)
PPT	Superolateral Patella	317.3 (170.2)	314.4 (153.7)	261 (138.4)	284.5 (150.1)
	Superomedial Patella	334.1 (147.4)	326.0 (149.9)	288.5 (132.3)	305.6 (141.3)
	Medial Joint line	355.1 (202.5)	318.7 (159.0)	298.5 (163.6)	308.7 (148.2)
	Tibialis Anterior Muscle	367.0 (182.4)	386.40 (175.8)	316.2 (155.4)	370.5 (157.4)
TS	Temporal Summation	1.8 (1.8)	2.30 (1.8)	2 (1.7)	2 (1.4)
CPM	Conditional Pain Modulation	52.8 (110.7)	53.4 (97.6)	48.2 (98)	29.4 (84.8)
Isokinetic Strength	Q60	69.4 (42.7)	79.52 (45.6)	73.7 (42.5)	88.7 (46.5)
	H60	52.19 (26.7)	54.44 (29.6)	55.86 (28.6)	64.9 (29.5)
	Q180	40.7 (26.1)	46.1 (28.8)	43.5 (29.4)	50.9 (26.6)
	H180	37.3 (21.2)	40.8 (22.5)	41.4 (24.2)	46.5 (21.9)
Sleep Traits		**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
	Time in bed	3.57 (2.89-4.56)	3.76 (3.06-4.42)	3.69 (3.03-4.24)	3.57 (2.99-4.17)
	Total Sleep Time	3.1 (2.42-3.95)	3.18 (2.63-3.82)	3.36 (2.5-3.66)	3.18 (2.4-3.56)
	Onset Latency	0.02 (0.01-0.03)	0.02 (0.01-0.03)	0.02 (0.01-0.03)	0.02 (0.02-0.03)
	WASO	0.43 (0.32-0.53)	0.44 (0.34-0.59)	0.42 (0.27-0.58)	0.48 (0.32-0.6)
	Sleep Efficiency	0.81 (0.74-0.86)	0.8 (0.73-0.84)	0.8 (0.75-0.83)	0.77 (0.71-0.85)

Table 3-4: Baseline and follow-up data for variables of both groups.

Abbreviations: 30CST, 30 second sit to stand test, counts the number of times the participant comes from a sitting position on a chair to a full standing position in 30 seconds; **CPM,** Conditioned pain modulation, ranges from 0 to maximum value measured in kilopascal (kPa); **Isokinetic Strength, Q60 & Q180,** the isokinetic peak torque of quadriceps muscles measured at 60 degrees/second and at 180 degrees/second respectively, **H60 & H180**, the isokinetic peak torque of hamstring muscles measured at 60 degrees/second and at 180 degrees/second respectively, presented in Newton meter (Nm); **MSK-HQ,** The Musculoskeletal Health Questionnaire, 14 questions scored on a scale of 0-4 (lower scores indicate lower levels of symptoms or physical disability), the total score is the sum of all items; **NRS,** Numerical Rating Scale, 0-10 where 0 is no pain and 10 is the worst pain imaginable; **PSQI,** Pittsburgh Sleep Quality Index, ranging from 0-21, high score indicating poor sleep quality; **Sleep Traits,** Time

in bed, Total sleep time, Onset latency, Wakefulness occluding after define sleep onset (WASO) and sleep efficiency, all scores showing hours, except sleep efficiency which is expressed in sleep efficiency in % divided by 100 (converted in to numbers); **PPT**, Pressure pain threshold, 0 to maximum value measured in kilopascal (kPa); **TS,** Temporal summation, ranges from 0 to 10 value on NRS; **TUAG,** Timed up and go test, measured in seconds, the participant stands up upon therapist's command, walks 3 meters, turns around, walks back to the chair and sits down**; WOMAC,** The Western Ontario and McMaster Universities Osteoarthritis Index, items are scored on a scale of 0-4 (lower scores indicate lower levels of Pain (5 items, 0-20), stiffness (2 items, 0-8), and physical function (17 items, 0-68).

Baseline and follow up values for different variables in each group have been shown in table 3-4 above. The usage of different types of medication at baseline is shown in Table 3-5. A Chi-squared test was utilised to assess any difference between both groups at baseline and at six weeks follow-up sessions. Table 3-5 denotes P-values (Chi-squared test), revealing no significant difference between both groups at baseline and at six weeks follow up.

Type of Medication	Control Arm (Frequency)	Control Arm (%) at baseline	Intervention Arm (Frequency)	Intervention Arm (%) at baseline	P-value at baseline	P-Value at 6 weeks
Topical Analgesics	1	1.7%	2	4.2%	0.47	0.12
Paracetamol	18	31%	10	20.8%	0.29	0.15
NSAIDs	8	13.8%	12	25%	0.20	0.29
Cox 2 inhibitors	1	1.7%	0	0%	0.36	0.36
Opioids	4	6.9%	5	10.4%	0.55	0.38
Opioids + Paracetamol	5	8.6%	5	10.4%	0.79	0.79
Neuropathic pain killers	9	15.5%	3	6.3%	0.15	0.10
Anti-depressant	3	5.2%	5	10.4%	0.34	0.34
Supplements	13	22.4%	8	16.7%	0.48	0.48

Table 3-5: Demographics of medication in both groups at baseline. Chi-squared test P-values are shown for both groups at baseline and at follow-up visits.

3.8 iBEAT-OA and Pain

3.8.1 Numerical Rating Scale (NRS)- Pain (Primary outcome)

The intervention group, but not the control group, improved the mean NRS pain score (-1.8 [95% CI -1.3 to -2.4] vs -0.3 [95% CI 0.2 to -0.8]) at the 6-week follow-up (Table 3-6). The mean between-group difference was 1.5 (95% CI -0.8 to -2.2, P =.0014). P-value is based on a two-tailed t-test. The graphical representation of change is shown in figure 3-2.

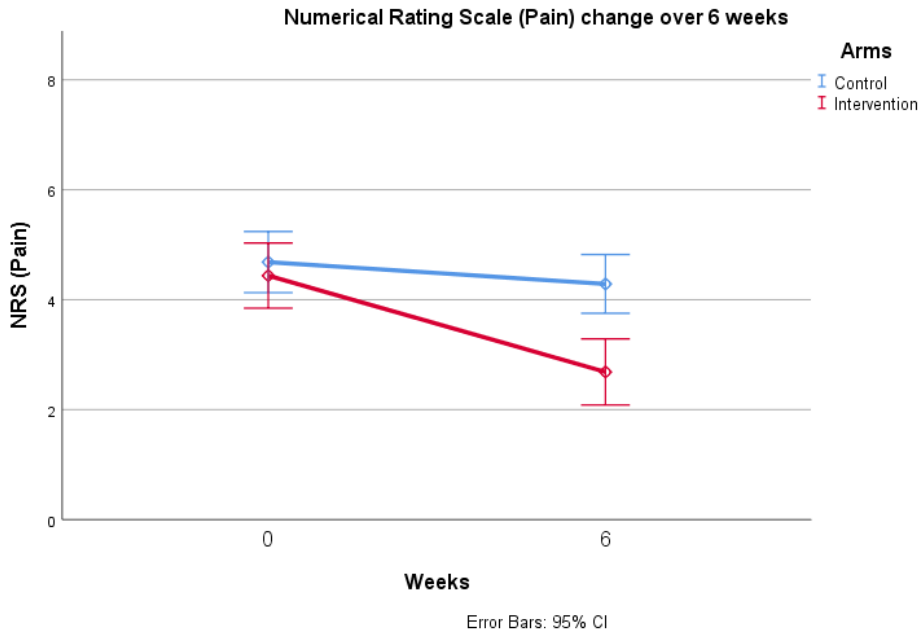


Figure 3-2: Change in Numerical Rating Scale (NRS) over time (baseline to week six).

A previous study on knee OA has reported that minimal clinical important difference (MCID) for NRS is 1.33 (Alghadir et al., 2018). 30 participants out of 49 (61.2%) have reported pain reduction more than MCID in the intervention group.

Outcome	Control Group change Mean (95% CI)	Intervention Group Change Mean (95% CI)	Difference in change Intervention Group- Control Group Mean (95% CI)	P-Value Between Group Analysis – Two tailed t-test	P-Value With-in intervention Group Analysis – Paired t-test
NRS pain	-0.3 (0.2;-0.8)	-1.8 (-1.3;-2.4)	-1.5 (-0.8;-2.2)	0.0014	0.0000
PPT					
Superolateral Patella	-55.6 (-25.2;-86.1)	-30.5 (2.6;-63.7)	25.1 (-19.9;70.1)	0.3	0.1
Superomedial Patella	-44.0 (-15.7;-72.4)	-22.3 (8.7;-53.2)	21.8 (-20.2;63.9)	0.3	0.2
Medial Joint line	-49.1(-16.7;-81.4)	-18.9 (16.4;-54.1)	30.2 (-17.8;78.2)	0.1	0.6
Tibialis Anterior Muscle	-54.6 (-23.0;-86.1)	-11.4 (23.0;-45.8)	43.2 (-3.6;89.9)	0.2	0.5
TS	0.1 (-0.3; 0.5)	-0.1 (0.4;-0.5)	-0.1 (0.4;-0.7)	0.2	0.3
CPM	-4.9 (19.5;-29.2)	-23.8 (2.8;-50.3)	-18.9 (17.2;-55.0)	0.5	0.1

Table 3-6: Results of Pain (NRS) and Quantitative Sensory Testing (QST) outcome measures. Abbreviations: CPM, Conditioned pain modulation, ranges from 0-maximum value measured in kilopascal (kPa); **NRS,** Numerical rating scale, 0-10 where 0 is no pain and 10 is the worst pain imaginable; **PPT,** Pressure pain threshold, 0 to maximum value measured in kilopascal (kPa); **TS,** Temporal summation, ranges from 0 to 10.

3.8.2 Quantitative Sensory Testing (PPT, TS and CPM)

There were no within-group changes or between-group differences of quantitative sensory testing (PPT, TS and CPM). The results are shown in Table 3-6. Deep diving of data suggests that both groups have increased sensitisation (PPT) around the joint when assessed over six weeks. This was evident with negative values of PPT in both groups indicating deterioration; however, more decline was observed in the control group. Interestingly, the least deterioration was seen around the muscle origin (tibialis anterior) compared to the knee joint (superolateral patella, superomedial patella and medial joint line); however, this reduction was only seen in the intervention group. The control group had shown a significant deterioration around the tibialis anterior and knee joint, though not statistically significant. The data suggested that participants became more sensitive to pressure around the knee joint and muscle (tibialis anterior). The results for CPM were similar and showed more sensitisation around the knee joint after six weeks.

The results of temporal summation showed that the intervention group improved at follow-up sessions (negative result indicated improvement); however, this improvement was not statistically significant between-group or within the group.

3.9 iBEAT-OA and Muscle Strength

The quadriceps and hamstrings strength at 60°/sec and 180°/sec angular velocities were secondary outcomes. The purpose of these was to see if 6-

weeks of web-based exercises gain objective improvement in muscles strength. The analysis showed a statistical difference in strength gains of hamstring muscle strength at 60°/sec (P=0.011) in the intervention group when between-group analyses were run (Table 3-7, Figure 3-3 and Figure 3-4). Additionally, there were strength gains of quadriceps muscles at 60°/sec (P=0.003) and hamstring muscles at 60° and 180°/sec (P<0.01 & P=0.001 respectively) when with-in intervention group paired t-test was conducted (Table 3-7).

Outcome	Sub score	Difference in change Intervention Group- Control Group Mean (95% CI); P-Value Between Group Analysis – Two tailed t-test	P-Value With-in intervention Group Analysis – paired t-test	Cohen's d Change Intervention group
Isokinetic Strength	Q60	5.7 (-1.4;-12.7) p=0.113	P=0.003	.20
	H60	6.9 (1.6;12.3) p=0.011	P=0.0000	.35
	Q180	2.7 (-3.3;8.6) p=0.377	P=0.07	.17
	H180	1.8 (-2.7;6.3) p=0.432	P=0.001	.26

Table 3-7: The outcome of the two-tailed t-test for muscle strength analysis between control and intervention groups and the paired t-test within the intervention group. Isokinetic Strength, Q60 & Q180, the isokinetic peak torque of quadriceps muscles measured at 60 degrees/second and at 180 degrees/second respectively, H60 & H180, the isokinetic peak torque of hamstring muscles measured at 60 degrees/second and at 180 degrees/second respectively, presented in Newton meter (Nm).

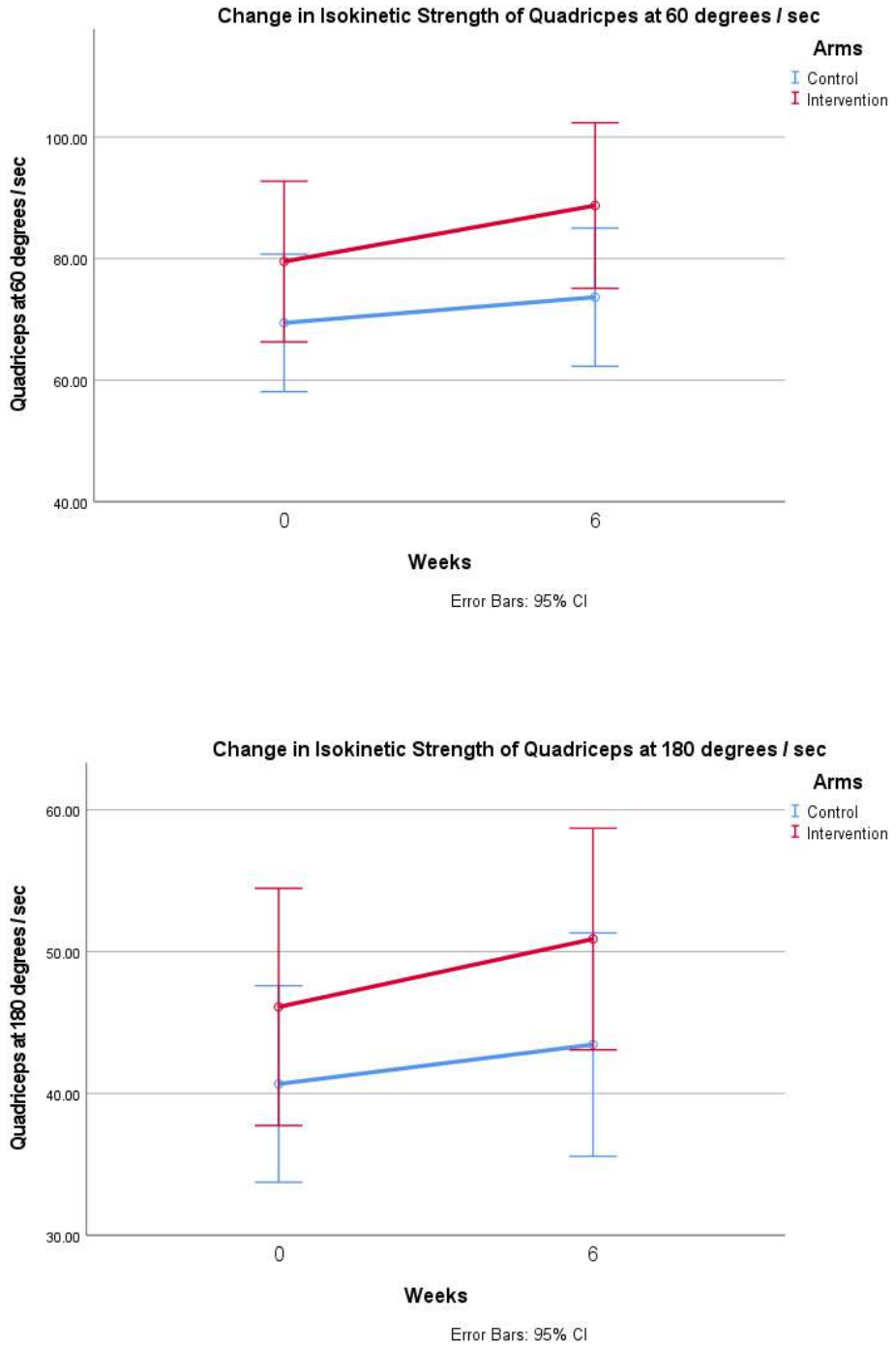
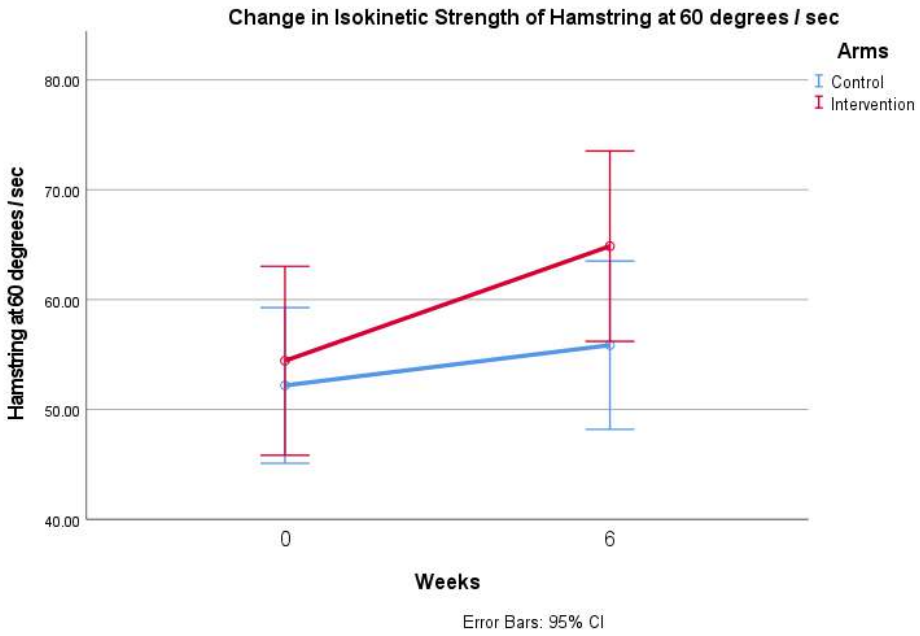


Figure 3-3: Change in Isokinetic strength of quadriceps at 60 degrees/sec and 180 degrees/sec over time (baseline to week six).



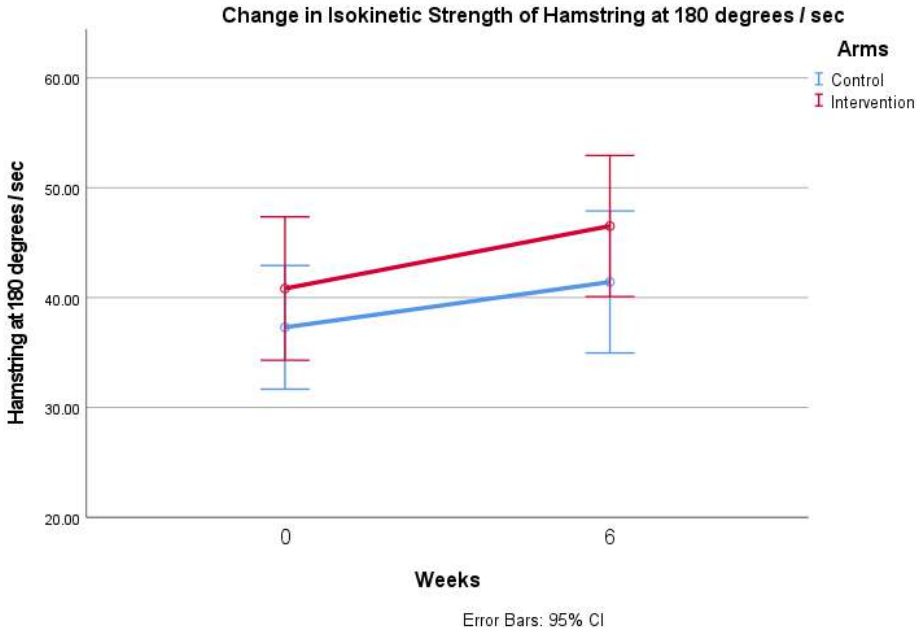


Figure 3-4: Change in Isokinetic strength of hamstring at 60 degrees/sec and 180 degrees/sec over time (baseline to week six).

3.10 iBEAT-OA and Muscle Thickness Assessment (MTA) of Vastus Lateralis Oblique (VLO) using MSK Ultrasound

The musculoskeletal ultrasound scan protocol written and used by the Physiology, Pharmacology and Neuroscience Division at the University of Nottingham (UoN) was used to gain the protocol approval for this study and assess Vastus Lateralis Oblique (VLO) muscle. The purpose of this was to determine the muscle strength based on the thickness gains in muscle fibres. Thus, the ultrasound scan could indirectly establish if the exercises had increased maximum voluntary contraction. The assessment procedure is explained in detail in the second chapter, section 2.12.3.

The research team and author were confident to follow the procedure following the approval of the study protocol. However, when I started pre-study trials to assess the muscles, it was found that the ultrasound machine at the department of rheumatology (Toshiba Aplio SSA-770A machine) had no panoramic function. This mode was essential to find the mid-line of vastus lateralis (from medial to lateral) and measure the thickness of VLO at the same point pre- and post-exercise. The assessment of the thickness of VLO was dropped from our study due to lack of equipment and due to the fact that I already measured the strength of quadriceps muscles with a dynamometer.

3.11 iBEAT-OA and MSK ultrasound (Effusion / Synovial hypertrophy)

The frequency of sonographic features for each group are shown in table 3-8, and there was no difference between groups pre- and post-intervention. The maximal synovial thickness and effusion depth were measured in millimetres using the longitudinal axis. These absolute values were dichotomised as absent (<4mm) or present (≥4mm) according to the EULAR Research Group recommendation (D'Agostino et al., 2005). The between-group analyses were run using the chi-squared test. The baseline and follow-up data and P-values are given in table 3-8.

	Control Arm baseline		Control Arm follow up		Intervention Arm baseline		Intervention Arm follow-up		P-value	
Sonographic Features	n	%	n	%	n	%	n	%	Baseline	Follow-up
Effusion	25	43.85	20	35.9	17	35.4	15	31.2	0.38	0.68
Synovial Hypertrophy	13	22.8	15	26.3	12	25.0	11	22.9	0.7	0.69

Table 3-8: Sonographic features of OA in the participants of iBEAT-OA RCT. Chi-squared test P-values for between-group differences are shown at baseline and follow-up visits.

The positive doppler was found in one participant who dropped out of study; therefore, doppler assessment was not possible.

Further exploratory analyses were performed measuring effusion and synovial hypertrophy in millimetres (continuous data) and comparing before and after intervention measurements using independent t-tests for these two variables.

The between-group analysis of mean change from baseline to 6 weeks showed no difference in effusion or synovial hypertrophy. The within-group analyses showed no changes in the effusion and synovial hypertrophy (Table 3-9).

Outcome	Difference in change Intervention Group-Control Group Mean (95% CI); P-Value Between Group Analysis – Two tailed t-test	P-Value With-in intervention Group Analysis – paired t-test; (95% CI)
Effusion	0.12 (0.9 to -1.2) p=0.8	p=0.9 (0.7 to -0.77)
Synovial Hypertrophy	-0.44 (-0.4 to 1.3) p=0.3	p=0.3 (-0.24 to 0.78)

Table 3-9: The outcome of Ultrasound analysis between control and intervention groups and with-in intervention group.

3.12 Results for Adherence

The participants in the intervention group were supposed to exercise daily, and the app monitored their compliance. The research team and author had no way to establish compliance other than relying on the data captured by the app. The participants were supposed to tick the 'completed' box after each set of exercises, educational sessions and functional activities before they were allowed to proceed to the next session. Once the participants had completed the whole session (given for that day), the app marked this as a completed session. The author (SG) relied on the information provided by JA, and limited data was available to the author (SG). Each participant was supposed to complete 42 sessions (6 weeks multiply by seven days), and compliance

provided to the author was based on completing the total number of sessions out of 42 sessions. This was supplied to the author in the form of each participant's percentage of the sessions completed. The intervention group's mean (SD) adherence was 87.9% (14.3). In the practical world, this means that each participant finished exercise sessions six days per week and missed one day of intervention per week on average. Thirty-one participants had 87.9% or above compliance, and two participants had compliance of less than 50 % (40.5% & 46.1%). These two participants were unique as they preferred to exercise on alternate days and sometimes missing two-three days of exercise.

3.13 Summary of Chapter Three

This RCT study showed that a digitally delivered first-line knee OA management programme (JA) was superior to routine self-managed care when the primary outcome pain was compared.

There was no between groups or with-in group difference seen in pain sensitivity when assessed over six weeks.

This study has shown that the intervention group had improved strength of hamstring at 60°/sec when compared to the control group, and the intervention group had shown strength gain of quadriceps at 60°/sec and hamstrings at 60° and 180°/sec angular velocities. Lastly, there was no difference in sonographic features of knee OA before and after exercise and between both arms at baseline and six-week follow-up.

Chapter 4 Sleep and Web-based Exercises

4.1 Introduction

Knee OA pain is accompanied by a number of additional disturbances that influence an individual's health. There is a known link between sleep disturbances and chronic pain (Wilcox et al., 2000, Power et al., 2005, Smith et al., 2009a, Campbell et al., 2015, Harrison et al., 2003, Doherty and Smith, 1993, Leigh et al., 1988). These studies confirmed that individuals with OA have higher suffering from sleep disturbances.

Sleeping is essential for good health and wellbeing (Kryger et al., 2017). The National Sleep Foundation recommends that individuals sleep for seven to nine hours (Hirshkowitz et al., 2015, Kovacevic et al., 2018). Sleep is an essential function that allows our body and brain to recharge and leaving us alert and refreshed when we wake up (Kryger et al., 2017). Lack of sleep can impair our brain and our abilities to function normally (NIH, 2020). Impaired sleep and sleep loss can lead to cognitive impairment, mood changes and hormonal imbalances (Dinges et al., 1997, Carskadon and Dement, 2005). This means that healthy sleep is critical for the retention of human performance and functions and hence studying sleep is essential when studying an exercise plan to manage knee OA.

Sleep disturbances have been recognised as an essential factor in determining pain perception in individuals (Campbell et al., 2015). A relationship between sleep disturbances and pain severity in knee OA patients is usually explored, and sleep disturbances such as shortened sleep duration and fragmented sleep (Wilcox et al., 2000) have been associated with increased sensitivity to pain in OA patients and consequently with decreased quality of life (Smith et

al., 2009a). Therefore, studying the sleeping pattern is highly relevant if we discuss a successful online exercise programme for knee OA. This study aimed to assess whether an online exercise program (JA App) improves sleep duration or reduce sleep fragmentation.

All participants were given an actigraphy device. The actigraphy device monitored the following sleep outcome measures:

4.1.1 Time in bed (TIB)

As the name indicates, this is the total time spent in the bed by participants while sleep monitoring equipment was worn and activated (Shrivastava et al., 2014, Reed and Sacco, 2016). This is an important factor as a participant who only spends three to four hours in bed cannot reasonably go through all normal stages and cycles of sleep.

4.1.2 Total Sleep Time (TST)

Refers to the total amount of sleep time scored. This is recorded as a time from sleep onset to sleep offset (Shrivastava et al., 2014, Reed and Sacco, 2016) and is quantified in minutes.

4.1.3 Onset Latency

This is defined as the duration of time between when the lights are turned off as the participant attempts to sleep until the time participant actually falls

asleep (Shrivastava et al., 2014, Reed and Sacco, 2016) and recorded in minutes. It is also known as sleep onset latency or sleep latency.

4.1.4 Wakefulness occurring After defined Sleep Onset (WASO)

It is defined as periods of wakefulness occurring after defined sleep onset and reflection of sleep fragmentation (Shrivastava et al., 2014, Reed and Sacco, 2016). It is recorded in minutes.

4.1.5 Sleep efficiency (SE)

This refers to the percentage of total time in bed actually spent in sleep (Shrivastava et al., 2014, Reed and Sacco, 2016). The total amount gives a general estimation of the overall quality of sleep. This provides a broad sense of how well a person slept, but it does not distinguish between frequent and brief episodes of wakefulness. This is usually used as an indicator of sleep quality (Said, 2013, Fetveit and Bjorvatn, 2006, Blytt et al., 2017). 80% or above is considered a good sleep efficiency (Landry et al., 2015, Chen et al., 2015a).

The clinical significance of these sleep outcome measures is given in Table 4-1.

Sleep Traits	Measured in	Clinical Significance	References
Time in Bed (TIB)	Minutes	A low TIB may support a diagnosis of insufficient sleep.	(Shrivastava et al., 2014, Reed and Sacco, 2016, Blytt et al., 2017)
Total Sleep Time (TST)	Minutes	A low TST may indicate that one slept for an insufficient period of time due to non-medical reasons, certain medical reasons or as a result of the effect of medication.	
Onset Latency	Minutes	Consistent onset latency indicates that the 'lights out' time was close to one's routine bedtime. If lights are turned out earlier than one's usual bedtime, this will increase. This indicates whether one is paying attention to pre-sleep preparation and consistent with sleep timings.	
Wakefulness occurring After defined Sleep Onset (WASO)	Minutes	This is a reflection of sleep fragmentation.	
Sleep Efficiency (SE)	Percentage (TST/TIB x 100)	A low SE could result from long sleep latency and long sleep offset to lights on time, otherwise normal quantity and quality of sleep in between.	

Table 4-1: Different variables of Sleep and their clinical significance

Other than actigraphy, I have used the Pittsburgh Sleep Quality Index (PSQI) questionnaire to monitor the subjective assessment of individuals monitoring their sleeping habits.

4.2 Aims

This chapter aims to establish whether physical exercise in people affected with knee OA improves sleep (time in bed, total sleep time, onset latency or sleep efficiency) or reduces WASO. Additionally, subjective self-assessment of sleep was monitored by research participants and responded to in the PSQI questionnaire. The hypothesis was based on the fact that exercise reduces pain, and sleep should also improve with this reduction of pain.

4.3 Statistical Analysis

The methods used are those explained in chapter 2. For actigraphy data, histograms did not show bell-shaped curves, and baseline data are shown in table 4.2.

		Control Group at baseline (n=57)	Intervention Group at baseline (n=48)	P-value (between group differences at baseline)
Outcome	Sub score	Median (IQR)	Median (IQR)	NA
Sleep Traits	Time in bed	3.57 (2.89-4.56)	3.76 (3.06-4.42)	p=0.81[a]
	Total Sleep Time	3.1 (2.42-3.95)	3.18 (2.63-3.82)	p=0.8[a]
	Onset Latency	0.02 (0.01-0.03)	0.02 (0.01-0.03)	p=0.58[a]
	WASO	0.43 (0.32-0.52)	0.44 (0.34-0.59)	p=0.41[a]
	Sleep Efficiency	0.81 (0.7-0.86)	0.8 (0.7-0.84)	p=0.39[a]
	PSQI	8.5 (3.7) [b]	9.18 (3.4) [b]	p=0.01[c]

Table 4.2: Baseline data for sleep variables of both groups and results of between-groups analyses at baseline.

Abbreviations: PSQI, Pittsburgh Sleep Quality Index, ranging from 0-21, high score indicating poor sleep quality; **Sleep Traits,** Time in bed, Total sleep time, Onset latency, Wakefulness occluding after define sleep onset (WASO) and sleep efficiency, all scores showing hours, except sleep efficiency which is expressed in sleep efficiency in percentage. [a] Mann-Whitney two-tailed test result, [b] Mean (SD), [c] two-tailed t-test result

On searching for normative values, values for different sleep parameters in the healthy population (Thurman et al., 2018), previous studies on various populations (Fekedulegn et al., 2020, Berger et al., 2005), population with knee OA and population with knee OA + insomnia (Campbell et al., 2015) are given in Table 4-3. The data collected by actigraphy was compared to normative values given in table 4-3. Comparing these values to those shown in Table 4-3 and after discussion with the manufacturer of the actigraphy devices used in my study (Condor instruments), it became apparent that the variables for "time in bed" and "total sleep time" had not been reliably captured by the devices

due to a potential technical issue but that 'Onset Latency, WASO & Sleep efficiency' were within range and reliable according to the manufacturer and published data from earlier studies. I, therefore, excluded the two variables following the manufacturer's suggestion from all further analyses.

	Normative values[1]	Values for knee OA population[2]	Values for knee OA+ Insomnia Population[2]	Values for healthy individual[3]
Sleep parameters	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Time in bed	Not given	Not given	Not given	Not given
Total Sleep Time	7-9 hours	4.96h (1.2)	5.1h (1.3)	7.09h (1.77)
Onset Latency	<20 minutes	0.24h (0.14)	0.44h (0.4)	0.51h (0.69)
WASO	<10% of total sleep time in minutes	2.05h (1.23)	2h (1.27)	0.95h (1.6)
Sleep Efficiency	≥80%	66% (0.1)	65% (0.2)	Not given

Table 4-3: Values for different sleep parameters given by literature.

1- **Based on data from studies Fekedulegn et al. (2020) & Berger et al. (2005)**
2- **Based on data from the study by Campbell et al. (2015)**
3- **Based on data from the study by Thurman et al. (2018)**

Because Onset Latency, WASO, and sleep efficiency variables are not normally distributed (see Histograms in appendix 4), I carried out a non-parametric analysis (Spearman's correlation) and found a significant association in Onset Latency only when score differences (follow-up minus baseline) between groups were compared (Table 4-4).

Change in sleep traits	Spearman's Correlations for change in sleep traits versus intervention – control arm	P-Values	95% confidence Interval
Difference between Onset Latency	0.2436	p=0.015*	0.05 - 0.42
Difference between WASO	-0.0465	p=0.646	-0.24 - 0.15
Difference between Sleep Efficiency	-0.0965	p=0.340	-0.28 - 0.1

Table 4-4: Spearman's Correlation Coefficient showing the associations observed between change in sleep parameters and arm of the intervention (Treatment =1 Control =0). The change in sleep parameters was computed as the difference of follow-up minus baseline sleeping parameters in both groups. *Statistically significant result.

The PSQI questionnaire's data distribution was normal (bell-shaped, Appendix 4), and I used two-sided t-tests for the PSQI questionnaire. The baseline values for PSQI are shown in Table 4-2.

4.4 Results

4.4.1 iBEAT-OA and Sleep assessed with actigraphy

For the actigraphy data, given the non-normal distribution of the data, I used a non-parametric test, specifically the Mann-Whitney two-tailed test for between-group analysis. The results are shown in Table 4-5. The results showed that the intervention group had deteriorated onset latency when compared between groups (Mann-Whitney two-tailed test). This analysis revealed that there was no difference in the change from baseline to follow up between arms in terms of WASO or sleep efficiency. Still, the data from the intervention suggested a

worsening of onset latency in the intervention group, which is statistically significant.

Change in sleep traits	Control Group at Follow-up (n=57)	Intervention Group at Follow-up (n=48)	Mann-Whitney Value	P-Values of two-tailed Mann-Whitney Test
Change in	Median (IQR)	Median (IQR)		
Onset Latency	-0.002 (-0.013 to 0.008)	0.002 (-0.003 to 0.012)	2324.5	p=0.015*
WASO	-0.006 (-0.097 to 0.081)	-0.048 (-0.096 to 0.090)	2743.5	p=0.65
Sleep Efficiency	-0.011 (-0.067 to 0.06)	-0.032 (-0.067 to 0.033)	2816	p=0.34

Table 4-5: Table showing follow-up data for sleep variables of both groups and results of Mann-Whitney two-sample test between intervention and control group. *Statistically significant result.

For comparison, normative values are given for sleep variables in table 4-3. On deep diving of data, 30 participants (52.6%) in the control group had good sleep efficiency (≥80%) at baseline, which was reduced to 24 participants (42.1%). Similarly, 25 participants (52%) in the intervention group had good sleep efficiency at baseline, which was reduced to 18 participants (37.5%) at follow-up post-intervention. These changes are not statistically significant, and therefore, it does not add any meaningful clinical context to the findings of our study.

4.4.2 iBEAT-OA and sleep assessed with PSQI

The baseline comparison between the two groups showed that the intervention arm had a worse self-reported PSQI score (higher score denotes poor sleep quality), and the comparison of both groups was statistically significant (P= 0.01), as shown in table 4-1. The participants in the intervention group felt that their sleep was disturbed at baseline. I do not have a valid way to establish why there was a difference in sleep quality at the baseline on PSQI. All other baseline demographics were similar for both groups, as reported in chapter 3. However, there was no difference (P=0.3) in PSQI overall score between groups post-intervention (Table 4-6).

Sleep Traits	Changes from baseline - Control arm mean (SD)	Changes from baseline - Intervention arm mean (SD)	Difference in change Intervention Group – Control Group Mean (95% CI) & P-Value between Group Analysis - Two tailed t-test
PSQI	-0.73 (2.6)	-1.27 (2.67)	-0.54 (-0.6; 1.6); p=0.3

Table 4-6: Changes in Pittsburgh Sleep Quality Index (PSQI) from baseline in both groups and results of two-tailed t-test denoting between-group analysis.

With-in group analysis showed that participants in the intervention group reported that they improved the quality of their sleep (question 1; subjective sleep quality [change from baseline: -0.42; 95%CI 0.1 to 0.7; P<0.01]), the percentage of time in bed that one sleeps (question 4; habitual sleep efficiency [change from baseline: -0.26; 95%CI 0.0 to 0.5; P=0.05]) and improved sleep disturbance (question 5; sleep disturbances [change from baseline: -0.29; 95%CI 0.1 to 0.5; P<0.01]). A lower score on PSQI means improvement;

therefore, the values for these three questions (mean change from baseline) are minus values.

4.5 Summary of Chapter Four

In order to evaluate if pain relief from exercise correlates with improvements in sleep quality, I assessed sleep measures at baseline and follow-up in the control and intervention arms by both actigraphy and a validated questionnaire. There was no improvement in sleeping traits when assessed via actigraphy. In fact, participants in the intervention group appeared to show a deterioration in the time required to sleep after getting into bed (onset latency). Using the validated questionnaire for sleep quality, some improvements were reported by participants in the exercise group, albeit only on some parameters, specifically, sleep quality, sleep efficiency and reduced sleep disturbances post-intervention. Further discussion on this is carried out in Chapter 6.

Chapter 5 Functional Activities and Web-based Exercises

5.1 Introduction

Two key intervention goals for the treatment of knee OA pain are relieving pain and reducing disability by improving functional abilities (Uthman et al., 2014). In this chapter, I will review first what is known regarding interventions to improve physical function in OA. Specifically, whether there is enough evidence regarding functional improvement due to routine face to face exercises and the evidence regarding digital health delivery of exercise programmes in terms of showing progress in the functional capacity. I will then discuss the results of the exercise intervention study in terms of functional improvement and the correlation between change in functions, pain and muscle strength and how these are associated and the potential causative links.

5.1.1 Evidence of the effect of exercise on functional disability

A previous systematic review with meta-analysis reported improvement in the overall functional capacity of participants with knee osteoarthritis and by exercising when compared to control group (Uthman et al., 2013, Li et al., 2016, Batterham et al., 2011). Uthman et al. (2013) reported that the combined intervention of strengthening, aerobics and flexibility exercise was significantly more beneficial than the control arm of no exercise. They reported an overall difference in function as −1.32 units (95% CI −2.44 to −0.21 units, medium effect size) on a WOMAC disability scale ranging from 0 to 10 for the combination of strengthening, aerobics, and flexibility exercise. They

concluded that this combination of earlier mentioned three types of exercise (71%) and/or aquatic strengthening plus aerobic exercises (71%) had the highest probability of being the best overall treatment for function. Due to the heterogenicity of exercises involved in this systematic review, they could not give precise details on strengthening, aerobics, and flexibility exercises. This meta-analysis has included trials with varying lengths of follow-up durations which might have introduced some heterogenicity into the network meta-analysis. They calculated the influence of differences in the duration of follow-up using meta-regression analysis, which did not result in significant differences in effect estimates.

Li et al. (2016) reported a moderate effect size (SMD: -0.53; 95% CI: -0.70 to -0.37; P<0.001) with resistance training for physical function improvement. They excluded non-English studies, and their analysis was not according to intention to treat (ITT), and these factors might have biased their results. Lastly, they excluded participants who underwent knee surgery or had severe knee arthritis, thus potentially exaggerating the outcomes.

Another systematic review and meta-analysis reported that exercise therapy has a moderate to large effect on increasing the total distance walked and gait speed (Tanaka et al., 2015). This study relied on the activity level, such as distance covered by participants. It included the studies where the physiotherapists assessed the participants rather than using a functional sub-scale of WOMAC (patient-reported measure). However, the evidence is either of low or moderate quality. Other limitations are the heterogeneity of age, types of exercises performed, and the amount of time spent walking (6 minutes to 60 minutes).

5.1.2 Digital health interventions

Most of these exercise programmes are offered individual-to-individual and not web-based. The ESCAPE (Enabling Self-management and Coping with Arthritic Pain using Exercise) reported functional improvement in group setup or individual exercises (Hurley et al., 2007); however, no study was conducted on the app version. Although there is data available for the efficacy of ESCAPE, but the app component has not been researched for its effectiveness. Another pilot study based on web-based physical activity intervention in patients with knee and hip OA reported improved physical function status (difference=6.5 points on Linkert based scale, 95% CI 1.8-11.2) compared with the control group. However, no effect was found when these groups were compared at 12 months intervals (Bossen et al., 2013). This study had a few flaws. Firstly, they recruited participants based on self-reported OA. The diagnosis was not verified with the clinical examination or x-rays. Additionally, the plan is based on a self-paced physical activity program in which the participant's favourite recreational activity is gradually increased. In a nutshell, the study from Bossen et al. (2013) is not based on the exercise programme.

A pilot study (Brooks et al., 2014) on web-based Therapeutic Exercise Resource Center (TERC) based on 65 participants reviewed over eight weeks follow-up reported improved physical function (sub-scale of WOMAC). As this was a pilot study, therefore limitations were small sample size and lack of control group. Also, mild-moderate knee OA were the inclusion criteria, limiting

the lesser active participants with severe OA from participation and potentially exaggerating results.

Another randomised controlled trial (Bennell et al., 2017) studying the effectiveness of internet-based exercises done on 148 participants reported significant improvement in pain (mean difference, 1.6 units on NRS [95% CI, 0.9 to 2.3 units]) and physical function (mean difference, 9.3 units on WOMAC physical function subscale [CI, 5.9 to 12.7 units]) than the control group at three months, and improvements were sustained at nine months (mean differences, 1.1 units [CI, 0.4 to 1.8 units] and 7.0 units [CI, 3.4 to 10.5 units], respectively). Over three months, they included seven skype sessions with the physiotherapists, an interactive automated pain-coping coach, and education material on exercise and physical activity. Participants were recommended to exercise three times per week. This study did not perform clinical assessment or radiographs similar to earlier mentioned studies to confirm knee OA. Also, they could not determine the contribution of each treatment component to achieve benefits or the minimum number of exercise sessions required for clinical effectiveness. The research team could not control for non-specific treatment effects.

To summarise, there is a lack of studies on online / web-based exercises that effectively improve the participants' functions.

5.1.3 Correlation between pain, muscle strength and functions

The second question concerns the correlation between pain around knee joint, functions and muscle strength and how these correlates. There is enough evidence for the effectiveness of exercises in the management of knee OA and to improve the functional capacity of these individuals to cope better with the activities of daily living (Bennell and Hinman, 2011, Messier et al., 2004, Thomas et al., 2002, van Baar et al., 1999, Chamberlain et al., 1982, Ettinger et al., 1997b, Ettinger et al., 1997a, Kovar et al., 1992, Minor et al., 1989, Fisher et al., 1991, Pisters et al., 2007, Hurley et al., 2007, Dunlop et al., 2011, Esser and Bailey, 2011, Lange et al., 2008). Despite strong evidence supporting the effectiveness of exercise as a treatment for knee OA, little is known about the mechanism supporting improvements in symptoms in people undergoing an exercise program (Runhaar et al., 2015).

It has been postulated that strengthening exercise program may provide several benefits to patients with knee OA, including facilitating endogenous opiates such as endorphin release, thus modulating pain (Stagg et al., 2011, Fraioli et al., 1980, Carr et al., 1981, Allen, 1983) and improving functional activities. This is one possible explanation of improved functional activities as a result of exercise. The other potential explanation of functional improvement is given by muscle strength gains around the knee joint. Evidence from observational studies (Ruhdorfer et al., 2016, Sanchez-Ramirez et al., 2015) and interventional studies (Baker et al., 2001, Knoop et al., 2015) reported an association between improvement in the strength of knee extensor muscles

and self-reported physical functions in patients with knee OA (Ruhdorfer et al., 2016, Sanchez-Ramirez et al., 2015, Baker et al., 2001, Knoop et al., 2015). This is not only limited to knee extensors, and another systematic review reported 60% and 71% of studies showing a significant change in knee extensor and knee flexor muscles from pre-to post-intervention, respectively (Runhaar et al., 2015). Another randomised controlled trial (RCT) reported that every 1-unit (Nm/kg) increase in knee extensor strength leads to 17 units (95% CI -29 to -5) improvement in physical function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Hall et al., 2017). This RCT has used a patient-reported functional improvement outcome measure (WOMAC), which is not based on the participants' physical performance, thus a limitation of this RCT. The question remains unanswered as to what improves the physical function in participants exercising for knee OA? Is it pain reduction or improvement in the strength of knee muscles?

Far and few studies have used analytical approaches to establish whether functional activities gain in patients with knee OA are due to pain modulation, muscle strengthening of knee extensor/ flexors, or a combination of both. One study used functional tests (a 2-minute walking test and a timed up and go test) and tried to answer the association between function improvement, muscle strength and pain (Bokaeian et al., 2018). They reported that a reduction in pain and improved functional activity occurs independently from increased quadriceps muscle strength in knee OA. The lack of a control group and small sample size (n=24) are two potential weaknesses of this study.

Another study tried to answer similar questions, and they reported that improved quadriceps muscle strength mediated the effects of strength on pain

and improved physical function (Hall et al., 2018). However, they used WOMAC function sub-scale instead of actual functional assessments and other potential mediators such as proprioception and pain medication were not assessed. Lastly, a small sample size (n = 49 in the strengthening group) is another potential limitation of this study. To conclude, there is a lack of high-quality studies which answers the question as to whether improvements in functional activities post-exercise regimen for knee OA are a result of the reduction in pain or a strength gain in knee muscles or potentially a combination of these two factors.

5.2 Aims

This chapter aims to establish two things based on the results of this study.

- Does the web-based intervention improve functional activities such as 30CST, TUAG and WOMAC – function subscale?
- What is the correlation between improvement in functions, pain and muscle strength? Does pain reduction in the joint correlate with improved functions, or does the gain in muscle strength improve functions? Understanding this complex relationship may help researchers and clinicians tailor an exercise program toward specific mechanistic factors, thus optimising treatment effects.

5.3 Results of Study

I will discuss the results of functional assessments such as 30 seconds sit to stand (30CST), Time up and go test (TUAG) and function sub-scale of WOMAC.

5.3.1 30 seconds sit to stand test (30CST)

The introduction and methodology of this functional test are described in Chapter 2. iBEAT-OA RCT showed that web-based exercises (JA app) significantly improved the 30CST in the intervention group (P<0.001) when compared to the control group (Table 5-1, Figure 5-1).

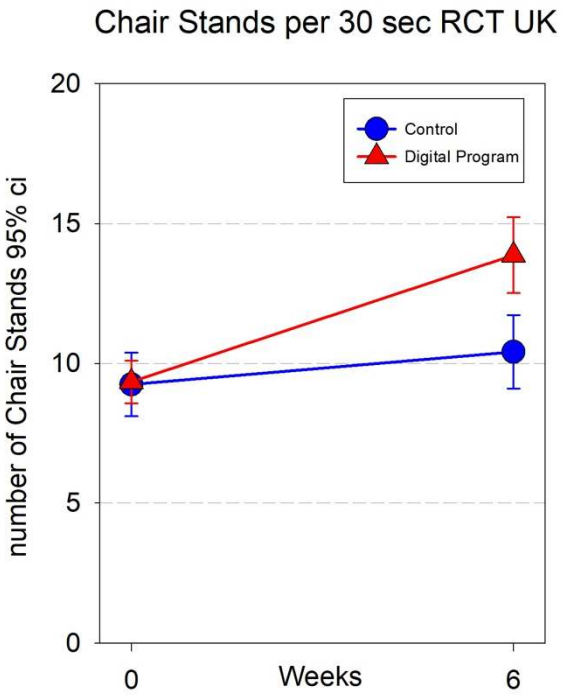


Figure 5-1: 30CST (30-sec sit to stand) difference in both groups over six weeks

Outcome	Difference in change Intervention Group-Control Group Mean (95% CI); P-Value Between Group Analysis – Two tailed t-test	Intervention group – Change from baseline (95% CI)- P-Value With-in intervention Group Analysis – paired t-test	Cohen's d Change Intervention group
30CST	3.4 (-2.2;-4.5) p=0.0001	4.5 (-3.7;-5.6) p=0.0000	1.24
TUAG	-1.8 (-0.5:-3.0) p=0.0105	-1.4 (0.5;2.3) p=0.0000	-0.76

Table 5-1: The outcome of two-tailed t-test for 30CST (30-second sit to stand test) and TUAG (Timed-up and Go test) between control and intervention groups and paired t-test with-in intervention group.

5.3.2 The Timed up and Go test (TUAG)

iBEAT-OA RCT showed that web-based exercises significantly reduced the TUAG of the intervention group (P=0.01) compared to the control group (Table 5-1, Figure 5-2).

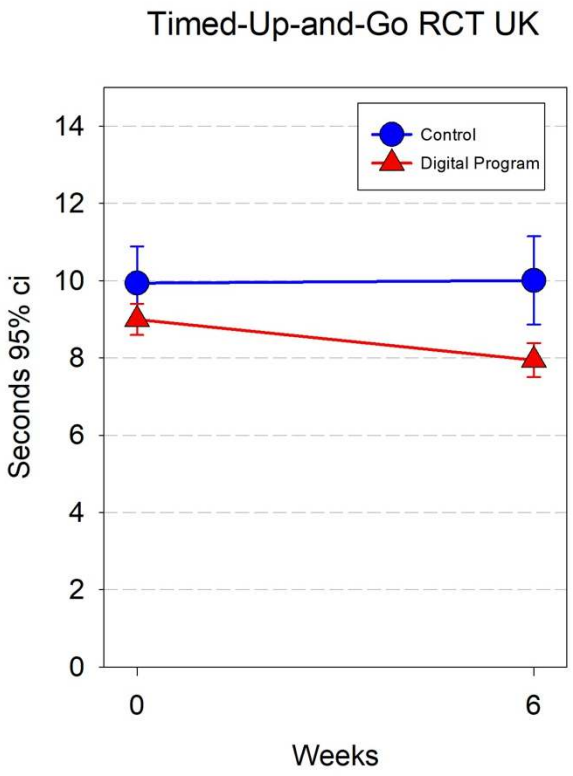


Figure 5-2: TUAG (Timed-up and Go) difference in both groups over six weeks

5.3.3 WOMAC and MSK-HQ

WOMAC is a self-administered questionnaire made of 24 items and consists of three subscales covering pain, stiffness and physical function. The physical function sub-scale consists of 17 questions and is scored from 0-68. A higher score means functional impairment, and a lower score indicates that there is an improvement. The between-group analysis of mean change from baseline to 6 weeks showed that the intervention group improved statistically significantly more than the control group in the WOMAC three subscales and overall WOMAC score (P=0.003) (Table 5-2 and Figure 5-3). Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

The within-group changes showed that the intervention group improved in all three WOMAC subscales (pain, stiffness and function) (P<0.01 for all three subscales), and there was no change on MSK-HQ.

Outcome	Subscore	Difference in change Intervention Group-Control Group Mean (95% CI); P-Value Between Group Analysis – Two tailed t-test	P-Value with-in intervention Group Analysis – paired t-test	Cohen's d Change Intervention group
WOMAC	Pain	-1.1 (-0.2;-2.0) p=0.0243	p=0.0000	-.60
	Stiffness	-1.0 (-0.5;-1.5) p=0.0000	p=0.0002	-.51
	Physical function	-3.4 (-0.7;-6.2) p=0.0417	p=0.0000	-.60
	Overall Score	-6.06 (-6.4;-10) p=0.0030	p=0.0000	-.57
MSK-HQ		-0.3 (-2.6;3.3) p=0.9	p=0.3	.11

Table 5-2: The outcome of two-tailed t-test for The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and The Musculoskeletal Health Questionnaire (MSK-HQ) between control and intervention groups and paired t-test with-in intervention group.

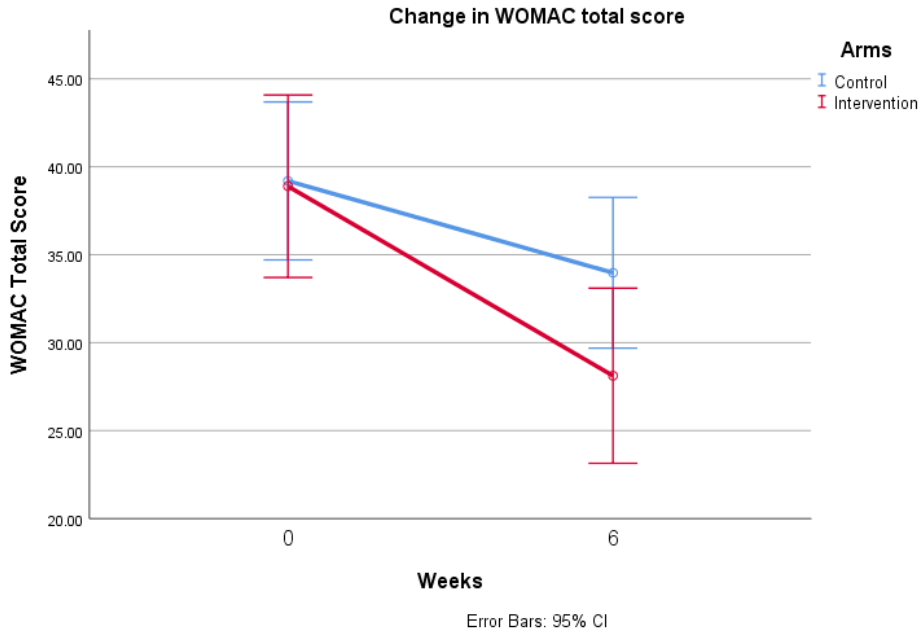


Figure 5-3: Change in The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) over time (baseline to week six).

MSK-HQ questionnaire consists of 14 questions, and all of these questions are summed together (response coded from 'not at all' = 4 to 'extremely' = 0, except for questions 12 and 13, which are coded in the reverse order), providing a total score from 0-56, with higher score indicating better MSK health. However, no change was seen on MSK-HQ (P=0.9) (Table 5-2).

5.4 Regression Analysis

The second question concerns the correlation between pain around the knee joint, functional improvement in participants and muscle strength and how these correlate, as discussed in section 5.1.3. I ran secondary exploratory analyses to find if I observe any correlation between improvements in pain, strength and functional activities.

The multiple regression analysis showed that the improvement in TUAG significantly correlated with hamstring muscle strength at 60°/sec (B= -0.048; 95%CI, -0.020 to -0.076, p=0.002), and 180°/sec (B= -0.086; 95% CI, -0.050 to -0.121, p<0.001), and quadriceps muscle strength at 180°/sec (B= -0.034; 95%CI, -0.004 to -0.064, p=0.029) when adjusted for age, gender, BMI, K/L scores and NRS. It indicated that improvement in TUAG functional ability was correlated with the improvement in quadriceps and hamstrings muscles. The reduction in NRS in the intervention group had no statistical correlation with the TUAG score (B= -0.087; 95%CI, -0.33 to 0.15, p=0.48), indicating that improvement in TUAG was not due to reduction in pain, albeit due to the strength gains which these participants had as a result of digital intervention.

Additionally, comparing the second variable for functional improvement (30CST) did not correlate with improved muscle strength around the knee joint or reduction in pain (Table 5-3). This is further discussed in chapter 6, section 6.7.

	Coefficient B	95% LCI	95% UCL	SE Coefficient	P Values
TUAG					
NRS	-0.087	-0.329	0.154	0.123	0.483
Q 60°/sec	-0.015	-0.041	0.011	0.013	0.275
H 60°/sec	-0.048	-0.076	-0.020	0.015	0.002
Q 180°/sec	-0.034	-0.064	-0.004	0.015	0.029
H 180°/sec	-0.086	-0.121	-0.050	0.018	0.000
30CST					
NRS	0.041	-0.461	0.543	0.256	0.874
Q 60°/sec	-0.033	-0.088	0.021	0.028	0.232
H 60°/sec	0.019	-0.047	0.085	0.034	0.576
Q 180°/sec	-0.039	-0.103	0.025	0.033	0.239
H 180°/sec	0.024	-0.067	0.115	0.046	0.614

Table 5-3: The outcome of Regression Analysis between pain, muscle strength and functional tests including TUAG and 30CST. Abbreviations: 30CST, 30 sec sit to stand test; **H 60°/sec** - isokinetic contraction of the hamstring muscle at 60°/sec angular velocity; **H 180°/sec** - isokinetic contraction of the hamstring muscle at 180°/sec angular velocity; **Q 60°/sec** - isokinetic contraction of the quadriceps muscle at 60°/sec angular velocity; **Q 180°/sec** - isokinetic contraction of the quadriceps muscle at 180°/sec angular velocity; **NRS**, Numerical Rating Scale; **TUAG**, timed up and go test.

5.5 Summary of Chapter Five

This study showed:

1- A web-based exercise programme can improve functional activities such as TUAG and 30CST.

2- Web-based exercise programme improved function sub-score of WOMAC.

3- The results showed a significant correlation between reduced TUAG scores in the exercise arm and improved muscles strength of the quadriceps (180°/sec) and hamstring (60°/sec and 180°/sec). The improvement in TUAG is only correlated with strength gains of quadriceps and hamstring muscles but not with the pain reduction.

4- The results did not show any correlation between 30CST, strength of muscles around knee or reduction in knee OA related pain.

Chapter 6 Discussion

6.1 Summary of findings of this study and the outcome of hypotheses

In this chapter, I review the objectives and hypotheses initially set out and assess whether the hypothesis can be accepted or rejected in light of the study findings. I also put the relevance of the findings of my research in the context of previous research, and novel findings of our study are discussed. The strengths and limitations are discussed, and I suggest potential future studies based on my research results and limitations.

6.1.1 Hypothesis 1: iBEAT-OA will reduce pain measured by NRS

The between-group analysis of NRS mean change from baseline to 6 weeks showed that the intervention group improved statistically significantly more than the control group. The mean between-group difference was 1.5 (P =.0014, 95% CI -0.8 to -2.2). My research suggests that six weeks of exercise intervention is useful to manage knee OA pain.

6.1.2 Hypothesis 2: iBEAT-OA will improve objective pain sensitivity assessment (QST)

There were no within-group changes or between-group differences of quantitative sensory testing (Pain pressure threshold [PPT], Temporal summation [TS] and Conditioned pain modulation [CPM]); therefore, this

hypothesis is rejected. The results of this RCT suggests that although we observed improvement in pain (NRS), the sensitivity of pain around the knee joint did not reduce within six weeks of exercising.

6.1.3 Hypothesis 3: iBEAT-OA will improve maximum voluntary contraction of Quadriceps and Hamstring muscles

There was a statistical difference in strength gains of hamstring muscle strength at 60°/sec (P=0.01, 95% CI 1.6 to 12.3) in the intervention group when between-group analyses were run. Additionally, there were strength gains of quadriceps muscles at 60°/sec (P=0.003, 95% CI -3.3 to -15.1) and hamstring muscles at 60°/sec (P<0.01, 95% CI -5.8 to -15.1) and 180°/sec (P=0.001, 95% CI -2.4 to -9.0) when with-in intervention group testings were conducted. The data of our study suggest that six weeks of online intervention gained strength in quadriceps and hamstring muscles in exercising participants.

6.1.4 Hypothesis 4: iBEAT-OA will improve functional assessment

The between-group analyses of mean change from baseline to 6 weeks showed that the intervention group improved statistically significantly more than the control group in 30CST (p<0.001, 95% CI -2.2 to -4.5) and TUAG (p=0.01, 95% -0.5 to -3.0). The data suggested that exercising participants

were more abled individuals to do certain functional activities, such as the number of times they stood in 30 seconds and increased gait speed between two points (TUAG). This was achieved in six weeks.

6.1.5 Hypothesis 5: iBEAT-OA will improve WOMAC and MSK-HQ

The between-group analyses of mean change from baseline to 6 weeks showed that the intervention group improved statistically significantly more than the control group in the WOMAC three subscales (P-value for pain = 0.02, 95%CI -0.2 to -2; P-value for stiffness <0.001, 95%CI -0.5 to -1.5; P-value for physical function = 0.04, 95% CI -0.7 to -6.2) and overall WOMAC score (P=0.003, 95% CI -6.4 to -10), however, no change was seen on MSK-HQ (P=0.9, 95% CI -2.6 to 3.3). This RCT suggests that exercising participants improved pain, stiffness and functions when assessed on a questionnaire (WOMAC); however, no significant difference was observed when a different questionnaire (MSK-HQ) evaluated their quality of life.

6.1.6 Hypothesis 6: iBEAT-OA will improve sleep quality and quantity in exercise group

The between-group analyses showed no improvement in sleep quality and quantity. In fact, the intervention group appeared to show a significant worsening in the amount of time it took them to fall asleep (onset latency), although this may be a spurious finding. Additionally, there was no

improvement (P=0.3, 95%CI -0.6 to 1.6) in PSQI score between-groups analysis. With-in group analyses showed that participants in the intervention group reported that they improved the quality of their sleep (question 1; subjective sleep quality; P<0.01, 95%CI 0.15 to 0.69), the percentage of time in bed that a person sleeps (question 4; habitual sleep efficiency; P=0.05, 95% CI 0 to 0.52) and improved sleep disturbance (question 5; sleep disturbances; P<0.01, 95% CI 0.12 to 0.45). The data suggested that participants who took part in the exercise arm did not improve their sleeping habits; however, exercising participants believed that their sleep was improved in some aspects (PSQI), including sleep quality and overall sleeping time.

The lack of improvement in objective sleep parameters is consistent with the lack of improvements in measures of central sensitization (see section 6.4). Sleep deficiency has been linked to chronic pain but specifically to aspects related to central processing of pain both in OA (Campbell et al., 2015) and other chronic pain conditions such as fibromyalgia (Siracusa et al., 2021). In spite finding clinically meaningful improvements in pain and function, I found no evidence of improvements in sleep or central sensitization, which suggests that the mechanisms involved in pain relief induced by muscle strengthening in this programme are separate from those relating to central processing of pain, which however affects only a subset of individuals with painful OA (Soni et al., 2019).

6.1.7 Hypothesis 7: iBEAT-OA will reduce sonographic features of inflammation (Effusion, synovial hypertrophy and hypervascularity)

The between and within-group analyses showed no change in sonographic features of knee OA; therefore, this hypothesis is rejected.

6.2 Novelty of this Study

This study is novel as to our knowledge; no study has yet evaluated a web-based intervention to improve knee OA in the United Kingdom, particularly as only individuals with radiographic evidence of knee OA were recruited, thus ruling out non-OA causes of knee pain such as soft tissue injury or patellofemoral syndrome as a sole reason for the knee pain.

Additionally, this study is unique to assess multiple factors, including pain, muscle strength, physical function, sonographic inflammatory features of OA and sleep. Our study is the first randomised control trial studying the functional benefits of the web-based program for knee OA having stringent eligibility criteria.

To our knowledge, no study has investigated the correlation between pain reduction, knee muscles strength improvement and physical functions assessed on 30CST and TUAG test without methodological flaws or inadequate sample size (chapter 1, table 1-1), which makes this study unique and novel. One of the novelties of this study is that hamstrings muscle strength

at 60 and 180°/sec speed correlated with improvement in TUAG testing other than quadriceps muscle strength at 180°/sec. In contrast, most previous studies were focused on strengthening quadriceps muscle alone for function improvement (Hall et al., 2018, Bokaeian et al., 2018, Runhaar et al., 2015). Our study reported that it is not only knee joint extensors strength, but the strength of knee flexors plays a vital role in improving functions in sufferers of knee OA. To conclude, the iBEAT-OA RCT has tried to explain the complex link between the strength of quadriceps, hamstring, physical function analysis and pain in the context of digital health interventions.

6.3 iBEAT-OA and Pain

Exercise interventions have been used to manage pain as a result of osteoarthritis, and there is ample evidence in favour of exercise intervention (Skou and Roos, 2019, Goh et al., 2019b, Gay et al., 2016, Fransen et al., 2015, Raposo et al., 2021, Juhl et al., 2014, Goh et al., 2019a). However, evidence is limited to eight studies assessing web-based delivery of exercise intervention for knee pain or osteoarthritis (Bennell et al., 2017, Mecklenburg et al., 2018, Lorig et al., 2008, Bossen et al., 2013, Kloek et al., 2018, Brooks et al., 2014, Dahlberg et al., 2016, Nero et al., 2017). These studies have been discussed in detail in section 1.10 and Table 1.1. Most of these studies reported a reduction in knee pain except Kolek et al. (2018), which reported no difference between web-based and face to face exercises. Their study used a pain sub-scale of Knee injury and Osteoarthritis Outcome Score (KOOS) rather than an isolated pain assessment tool. They had five face-to-face sessions and

35% dropouts at 12 months, thus potentially limiting or undermining the findings of their study. Compared to previous studies on web-based intervention, the results of iBEAT-OA RCT showed 41% improvement in NRS and 27.5% on pain sub-scale of WOMAC in the intervention arm over six weeks.

The minimally important change or difference between treatments, and responder criteria, are debated, and complex concepts challenging their application (Pham et al., 2004, Devji et al., 2017, MacKay et al., 2019). A previous study on knee OA has shown that minimal clinical important difference (MCID) for NRS is 1.33 (Alghadir et al., 2018). This RCT has demonstrated a mean difference of 1.8 on NRS in the intervention group, above MCID.

iBEAT-OA RCT used the JA app, and exercises used in this intervention were based primarily on strengthening quadriceps, hamstrings and muscles around the hips, and aerobics exercises were not involved in this intervention. Therefore, this intervention primarily focuses on a single intervention that strengthens muscles around the knee and hip joints. This RCT observed a significant improvement in pain (NRS) and pain sub-scale of WOMAC over six weeks. This study suggests that strengthening exercises delivered digitally are beneficial to reduce or manage knee pain in the sufferers of knee OA. The caution here is our study's high adherence rate, which has to be followed if one wants to reduce knee pain in six weeks by doing a web-based exercise programme. The results of our study are in agreement with previous systematic review and meta-regression based on 48 RCTs with a total of more than 4000 participants (Juhl et al., 2014). They concluded that exercise interventions focused on a single type of exercise were more effective in reducing pain than

those combining several types of exercise with different goals within the same session. Their stratified meta-analysis reported slightly more effect size for aerobics exercises (SMD 0.67 for pain) than strengthening exercises (SMD 0.62 for pain). Further stratified analyses showed that exercise interventions aiming on quadriceps strength only were more advantageous in reducing pain than interventions aimed at improving overall lower limb strength (SMD 0.85 [95% CI 0.55, 1.14], I^2 = 77.0% versus 0.39 [95% CI 0.27, 0.52], I^2 = 5.7%) (P = 0.005). In comparison, our study used strengthening exercises focusing primarily on knee extensors (quadriceps) and flexors (hamstrings), and a secondary focus was on hip muscles.

The significance of concentrating on one type of exercise is supported by earlier published meta-analyses (Jansen et al., 2011, Escalante et al., 2010, Juhl et al., 2014). At a physiological level, strengthening exercises increase the myofibrillar protein response, and aerobic exercises increase the content of mitochondria in the muscle (Juhl et al., 2014). The most commonly accepted justification for improving muscle strength is an initial neuromuscular response in the early stages of a training program, followed later by muscle hypertrophy (Folland and Williams, 2007, Pareja-Blanco et al., 2020). A meta-analysis consisted of 21 studies examining aerobic, and resistance exercise interference reported that the effect size for muscle hypertrophy is larger in strength training alone than in concurrent strength and endurance training (Wilson et al., 2012). When both aerobic and resistance exercise were performed within the same session, it reduced molecular response (myofibrillar protein response and the content of mitochondria) (Hawley, 2009) and hence

the suggestion to focus on one type of exercise intervention in one session (Jansen et al., 2011, Escalante et al., 2010, Juhl et al., 2014).

The general pain relief following exercise therapy could be due to pain gate control mechanism (peripheral synaptic decrease in pain fibre action potential due to motor neuron activity) (Wall, 1978, Ropero Peláez and Taniguchi, 2016, Hodges and Tucker, 2011) or central release of endorphins (Schwarz and Kindermann, 1992, Scheef et al., 2012). Both explanations relate to the amount and type of exercise done (Juhl et al., 2014), where strengthening exercise interventions favour pain gate control mechanism, and aerobics intervention suggest more involvement of central release of endorphins. Juhl et al. (2014) recommended that a minimum of exercising three times a week and at least 12 supervised sessions (4 weeks of intervention if three sessions per week are done) seemed to be essential and effective for pain relief. However, greater exercise intensity did not improve the effect of exercise interventions, as seen in direct comparisons in RCTs between high- and low-intensity exercise in aerobic and resistance training (Jan et al., 2008, Mangione et al., 1999), suggesting the need for other theories to describe the effect of exercise therapy in reducing pain (Juhl et al., 2014).

In comparison to Juhl et al. (2014) review, a recent systematic review and network analysis reviewed 103 trials (n=9134) (Goh et al., 2019b). They compared strengthening, aerobics, flexibility, mind-body (tai chi or yoga) and a 'mixed' exercise categories. Their primary outcome of interest was pain, and they reported that aerobic exercises were most beneficial for pain (ES 1.11; 95% CI: 0.69-1.54). Compared to aerobics, strengthening exercises had a moderate ES for pain (ES 0.73; 95% CI: 0.49, 0.98). The effect sizes (Cohen's

d) attained with iBEAT-OA RCT (d=-0.83; table 3-6 in chapter 3) corresponds to large effect size and are comparable to or greater than those presented in systematic reviews of face-to-face exercise programmes (Fransen et al., 2015, Thorstensson et al., 2015, Goh et al., 2019b, Juhl et al., 2014).

Another recent systematic review and meta-analysis based on 77 RCTs and 6742 participants reported that the efficacy of exercise over usual care was generally greatest at two months after starting exercise and was gradually reduced over time to become no better than routine care at 9 to 18 months when compared for pain, function and performance (Goh et al., 2019a). Based on their findings and the fact that our intervention lasted for six weeks only, we might have seen further improvement in pain if this intervention was carried out for eight weeks. Additionally, Goh et al. (2019a) reported that trials in which participants were younger and not waiting for knee replacement surgery reported better pain relief after the intervention. Although I do not have data suggesting the number of participants waiting for knee replacement in this RCT, however, if I assume that participants with a radiographic score of K/L=4 were potentially waiting for knee replacement procedure, then 10% of participants in each group fall into that criterion, indicating that 90% of participants in each group were not due for knee replacement surgery. This might be a potential reason for seeing a significant improvement in pain outcomes (NRS and pain sub-scale of WOMAC).

The results of this RCT are consistent with studies of other chronic conditions showing efficacy and effectiveness of digital management (Castro Sweet et al., 2018, Toelle et al., 2019, Shebib et al., 2019). Advantages of a digitally delivered treatment may include beneficial outcomes and lower costs, and

easier access for patients living in remote areas where transport may be an added obstacle. In a pandemic such as the current Covid-19, digital care can be beneficial regarding providing and continuing exercise programmes without interruption.

6.4 iBEAT-OA and QST

There was no within-group or between-group statistically significant improvement in quantitative sensory testing (PPT, TS and CPM). The data from iBEAT-OA RCT suggested that both groups had increased sensitisation (PPT) around the knee joint when assessed over six weeks. However, less deterioration was seen in the intervention group and least around the tibialis anterior muscle than knee joint (medial, supero-lateral and supero-medial). A similar observation was seen for the results of CPM, and it revealed more sensitivity around the knee joint in both groups at follow-up sessions. There may be few explanations of this phenomenon. Firstly, our study was not powered for QST, so our sample might not be enough to detect a significant difference in either direction.

Secondly, previous studies have shown a transient acute increase in sensitivity of QST with increased activity (Burrows et al., 2020, Murphy et al., 2008, Wideman et al., 2014). A recent cross-sectional study (n=31) examined the relationship between physical activity and pain in knee OA patients (Burrows et al., 2020). These participants underwent assessments of symptoms via self-reported questionnaires and QST. The physical activity and symptoms were monitored for seven days using accelerometers and logbooks. Cross-

correlation analyses were completed on variations in symptoms and physical activities across the week to identify the relative timing of the strongest association between pain and exercise. Their analyses of the temporal relationship between pain and physical activities across days predominantly showed that pain was worsened by periods of increased physical activity. They concluded that acute exercise might transiently worsen pain sensitisation in people with knee OA but being more physically active is negatively associated with pain in the absence of recent physical activity. The findings of their study were supported by the results of their meta-analysis of 13 studies (n=9,363), which detected considerable heterogeneity for associations between physical activity and pain (I^2 = 91.2%), ranging from positive to negative correlations. Considering their findings, the control group in our study might have deteriorated due to lack of exercise. In contrast, the intervention group might have worsened sensitisation due to acute exacerbation as a result of exercising daily. As I do not have weekly QST data to run cross-section analyses, therefore, the temporal relationship for increased sensitisation is just another question which this study has posed. Although participants in this RCT felt that their pain (NRS) improved around the knee joint in the intervention group, however their pain sensitivity around the knee joint did not improve statistically. However, the temporal summation (TS) results showed that the intervention group improved over six weeks (negative results indicated improvement), which was not statistically significant between groups.

The relationship between pain and exercise is reported to be bi-directional, and higher pain levels predict lower physical activity levels, whereas higher levels of physical activity predict less pain (Rabbitts et al., 2014); therefore, it would

be interesting to run this intervention on a long-term basis to establish whether QST would improve over time. This indicates a potential direction for future studies and assessing QST more frequently.

Finally, as discussed under section 6.1.6, the lack of improvement in either measure of pressure pain thresholds (PPT & CPM) is consistent with the lack of improvement in sleep quantity/quality measured by actigraphy, both of which have been linked to chronic pain in cases where central sensitization is involved (Campbell et al., 2015, Choy, 2015).

6.5 iBEAT-OA and improvement in muscle strength

Previous studies have reported strength improvement of the quadriceps muscles following exercise intervention when assessed using a handheld or standalone laboratory dynamometer (Suzuki et al., 2019, Luc-Harkey et al., 2018, Hall et al., 2018, Pua et al., 2011, Wang et al., 2007). However, there is no study assessing the strength of muscles around the knee following a web-based digital intervention. The iBEAT-OA RCT is unique in evaluating the strength of quadriceps and hamstring muscles using a standalone laboratory dynamometer.

Goh et al. (2019b) conducted a systematic review and network meta-analysis reviewing 103 trials (n=9134) and reported that strengthening exercises had a moderate effect size (ES) for pain (ES 0.73; 95% CI: 0.49, 0.98). Strengthening exercises increase the sarcomere protein response (Juhl et al., 2014) and early neuromuscular response is followed by muscle hyperplasia achieved during

strengthening (Folland and Williams, 2007, Pareja-Blanco et al., 2020). The pain gate mechanism explains the reduction in pain relief following strengthening exercise (Wall, 1978, Juhl et al., 2014, Ropero Peláez and Taniguchi, 2016). This is not limited to this theory only. There are suggestions to explore other explanations to describe the effect of exercise therapy in reducing pain (Juhl et al., 2014).

iBEAT-OA RCT has shown between-group strength gains in hamstring muscles strength at 60°/sec and with-in intervention group strength gains of quadriceps muscles at 60°/sec and hamstring muscles at 60°/sec and 180°/sec. The intervention arm had shown improvement of 19.2% in hamstring strength at 60°/sec, 14% in hamstring strength at 180°/sec, 11.5% in quadriceps strength at 60°/sec and 10.4% in quadriceps strength at 180°/sec. The results correspond to very small to small effect size (Cohen's d ranging from 0.17 to 0.35 , Table 3-7). As there is no other study on a digital intervention that has reported strength gain on the dynamometer, we do not have data to compare with other studies. To conclude, iBEAT-OA RCT results have shown that digital intervention for six weeks can improve muscles strength of the quadriceps and hamstrings.

6.6 iBEAT-OA and improved Functional Activities

Knee OA is a common form of arthritis globally (Felson, 1996, Neogi and Zhang, 2013, Reynaud et al., 2020). There is no cure for OA, and exercise therapy is considered as one of the core treatments (Goh et al., 2019b, Bannuru et al., 2019, Kolasinski et al., 2020, Skou and Roos, 2019, Wellsandt

and Golightly, 2018, Bartholdy et al., 2017). The primary goal of knee OA treatment is to reduce pain and improve functional capacity (Uthman et al., 2013, Goh et al., 2019b). There are multiple studies (Goh et al., 2019b, Bannuru et al., 2019, Kolasinski et al., 2020, Skou and Roos, 2019, Wellsandt and Golightly, 2018, Bartholdy et al., 2017), including RCTs and meta-analyses, which suggested that exercises for knee/hip improve the functional abilities of the participants; however, there is a lack of web-based exercises showing the efficacy of knee strengthening to enhance functions. As discussed in chapter 5, only limited studies have investigated the benefits of web-based exercises on functional activities (Brooks et al., 2014, Bennell et al., 2017). The first study by Brooks et al. (2014) was a pilot study with a small sample size and lacking a control group. It included participants with mild-moderate OA, thus limiting the generalisation of their results to the broader population, specifically on severe knee OA patients. The second study was RCT with 74 participants in the intervention arm reporting improved physical function (mean difference, 9.3 units on WOMAC physical function subscale [CI, 5.9 to 12.7 units]) than the control group at three months (Bennell et al., 2017). They had few limitations, including participants with chronic knee pain, lack of blinding, $50AUD gift vouchers as an incentive to complete study, and higher education level in the intervention group. Limited studies with flaws implied that a well-designed study was needed to evaluate functions in web-based exercise interventions without significant flaws and reasonable sample size. iBEAT-OA RCT tried to address previous shortcomings as discussed in chapter one and showed improvements on TUAG and 30CST tests, as shown in Table 5-1.

Reviewing normative values for 30CST, a previous study has reported 7.3 (SD2.8) repetitions of stands for hip and knee OA participants who were mobile independently and awaiting hip and knee replacement (Wright et al., 2011). In comparison, both groups in iBEAT-OA RCT had slightly higher repetitions at baseline (9.2 for control and 9.3 for intervention group), and both improved it to 10.3 and 13.8, respectively.

The normative value of >10 seconds for TUAG is reported for the elderly population with hip (Arnold and Faulkner, 2007) and knee (Alghadir et al., 2015) osteoarthritis. Interestingly, both groups in iBEAT-OA RCT had better baseline scores for TUAG than previous studies, and the control group deteriorated TUAG by 0.4 seconds, whereas the exercise group improved it by 1.4 seconds.

Previous studies on knee OA has shown MCID of 1.1 sec for TUAG (Alghadir et al., 2015) and 2.1 repetitions on the 30CST test (Wright et al., 2011), although the latter study was done on hip OA. There is a lack of study assessing MCID for 30CST in knee OA patients, and hence the reference for the hip study has been used. Our study has shown an improvement of 1.4 seconds on the TUAG test and 4.5 repetitions on 30 CST (Table 5-1), and these are above MCID mentioned earlier.

iBEAT-OA RCT has shown improvement on functional activities (TUAG -16%, and 30CST +48%), with standardised effect sizes (Cohen's d for TUAG= -0.76 and 30CST= 1.24; table 5-1 & 5-2) corresponding to medium to very large effect size.

The study I carried out is the first randomised control trial studying the functional benefits of the web-based program for knee OA having stringent eligibility criteria. This study showed that the web-based exercises for lower limb strengthening and education on OA could improve participants' functional abilities, including transfers such as sit to stand and timed up and go. Moreover, the participants reported improved scores on the function sub-scale of WOMAC. The results of our study are consistent with the findings of previous studies (Bossen et al., 2013, Brooks et al., 2014, Hall et al., 2017) that digital intervention can improve functions in participants with knee OA. Based on improved functional activities, these participants will transfer and walk quicker in the practical world and feel more confident.

6.7 Improved functional activities due to the reduction in pain or improvement in muscle strength?

Although it is assumed that exercise improves pain conditioning and strength of muscles around the knee, leading to improved functions, however, there is very little known about the causative factors influencing functional improvement. Despite the availability of a high number of studies, the association between exercise for knee OA, pain reduction, knee joint muscles strength and functional improvement is a puzzle for researchers (Runhaar et al., 2015). This study attempts to explain the improvement in functional assessments (TUAG and 30CST) and if they correlate with the strength

improvement in muscles around the knee joint and/or pain improvement in the knee joint.

The results showed a significant correlation between reduced TUAG scores in the exercise arm and improved muscles strength of the quadriceps (180°/sec) and hamstring (60°/sec and 180°/sec). Although the intervention arm has shown reduced pain and improved hamstrings strength (60°/sec) post six weeks of exercise regimen compared to the control group, however, the improvement in TUAG is only correlated with strength gains of quadriceps and hamstring muscles but not with the pain reduction (Chapter 5, section 5.4). The findings of this study have emphasised the importance of strengthening the muscles around the knee joint at moderate speed (60°/sec) and high speed (180°/sec) muscle training. One of the novelties of this study is that hamstrings muscle strength at both speeds correlated with improvement in TUAG testing. In contrast, most previous studies were focused on strengthening quadriceps for function improvement (Hall et al., 2018, Bokaeian et al., 2018, Runhaar et al., 2015). This piece of information will be helpful to physiotherapists and rehabilitation professionals, and the practical implication is essentially focusing on strengthening knee flexors and extensor muscles at various speeds when the goal of patients is to improve their functions.

Although the intervention arm had shown statistically significant improvement on 30CST compared to the control arm after six weeks of exercise intervention, I could not find any correlation between 30CST, muscle strength of quadriceps/hamstrings, and pain. This does not mean that there is no relationship between these; however, this may suggest that the relationship is more complex than just these factors. There may be additional factors involved

explaining improvement in 30CST. These additional factors may be the endurance of knee joint muscles, proprioception (Runhaar et al., 2015, Beckwée et al., 2013), kinematics of knee joint during sit to stand process (Bouchouras et al., 2015, Hoglund et al., 2014), and balance of the participants (Greve et al., 2019). Studying and correlating these additional factors may give us more insight into correlated factors with improvement in 30CST.

To the best of my knowledge, no study has investigated the correlation between pain reduction, knee muscles strength improvements and physical functions assessed on physical tests without methodological flaws or inadequate sample size. One previous study (Bokaeian et al., 2018) tried to explain the causative factors responsible for improving functions and concluded that strength gains in quadriceps were not correlated with the improvements in TUAG. This study had no control arm. A sample size of 24 volunteers indicated a potential reason their research failed to show a correlation between muscle strength and improvement in functions.

Another study tried to answer similar questions by secondary analysis (Hall et al., 2018); however, they did not use physical tests for functional assessment. Instead, they relied on the self-reported function sub-scale of WOMAC. They had a sample size of 49 participants in the intervention group (97 overall sample size). They used mediation analysis and concluded that increased knee extensor strength partially mediated improvement in physical function; however, the confidence interval for this estimate was very wide (95% CI, −192% to 356%), indicating the imprecision of their estimate.

In conclusion, iBEAT-OA RCT suggests that strengthening quadriceps and hamstring muscles improves physical function such as TUAG, which is essential for standing and walking in sufferers of knee OA. The improvement in physical function is explained by enhancing the strength of muscles around the knee joint instead of reducing knee joint pain. Understanding this complex relationship will help people with knee OA, researchers and clinicians to focus on exercise programs to strengthen knee extensors and flexors, especially if the overall goal is to improve the functions of people with knee OA. Further research is required to confirm these findings in long term exercise programs and investigate the dose-response relationship between muscle strength gains and improvement in physical functions.

6.8 iBEAT-OA, WOMAC and MSK-HQ

iBEAT-OA RCT has shown a significant improvement on the WOMAC questionnaire. WOMAC pain and function sub-scales results are consistent with the finding of function objective tests 30CST, TUAG and NRS scores. This intervention reduced pain and improved functions objectively (30CST, TUAG) and subjectively (WOMAC).

Multiple studies have used WOMAC as an outcome measure when assessing the benefits of exercises on participants with knee OA (Hughes et al., 2006, Bennell et al., 2016, Savik et al., 2014, Bennell et al., 2014, Schlenk et al., 2011). A previous RCT based on flexibility, aerobic walking, and resistance training with education under the supervision of physiotherapists reported 23%, 17%, and 23% on pain, stiffness and function WOMAC sub-scale respectively

at the end of an 8-week exercise (Hughes et al., 2006). A Cochrane review comparing 13 studies on exercise intervention (n=1599 with knee, hip or knee and hip OA) reported improved physical function by an absolute percent of 5.6% (95% CI -7.6% to 2.0%; SMD -0.27, 95% CI -0.37 to -0.17) (Hurley et al., 2018). Another recent systematic review that included 12 high-quality studies reported six studies with 297 participants demonstrated that resistance training was associated with a large effect size for the WOMAC pain subscale (Turner et al., 2020). Similarly, six studies showed that resistance training had a large effect size for WOMAC physical function sub-scale.

Only two previous studies on web-based intervention have included WOMAC as an outcome measure and reported improvement on the WOMAC questionnaire (Bennell et al., 2017, Brooks et al., 2014). Books et al. (2014) used a modified short version of WOMAC, and hence direct comparison of WOMAC results is not possible. Their study observed significant improvement on the WOMAC questionnaire, and a similar trend is seen in iBEAT-OA RCT. Bennell et al. (2017) reported a gain of 9.3 units (CI, 5.9 to 12.7 units) on the physical function sub-scale of WOMAC at three months follow-up compared to the control group. In comparison, our study has shown an improvement of 6.06 units (CI, 6.6 to 10 units) on physical function sub-scale of WOMAC compared to the control group at six weeks.

iBEAT-OA has shown 30.4% improvement on overall WOMAC score (Pain 27.5%, stiffness, 20%, physical function 27%) in the intervention group, with standardised effect sizes corresponding to medium effect size (table 5-2). A previous study has reported MCID of 6 for WOMAC physical function (Bennell et al., 2017). Our intervention group has shown a difference of 7.8 on WOMAC

physical function, which exceeds MCID threshold. Similarly, the intervention arm has shown a difference of 11.4 units on WOMAC overall score, which exceeds MCID of 10 units (Clement et al., 2018).

I could not see a statistically significant difference in MSK-HQ, and there may be several reasons for this. Firstly, this questionnaire is relatively new, and calculations are based on overall score of multiple factors, including pain, stiffness, sleep, quality of life, generalised well-being, and understanding of the diagnosis and treatment. It means that participants must improve on all these factors to see a statistically significant difference in the overall score. While iBEAT-OA RCT has shown improvement in pain, muscle strength and functional activities, it is yet to prove its effectiveness on other variables. Although this study is not focused on MSK-HQ, it highlights one of the weaknesses of MSK-HQ that an intervention should improve all the questionnaire contents for it to be statistically significant. Other established weaknesses of this questionnaire are the lack of rules for missing items and minimal clinically important differences (Hill et al., 2016b).

6.9 iBEAT-OA and Sleep

Sleeping enough is essential for good health and wellbeing. The National Sleep Foundation recommends that individuals sleep for seven to nine hours (Hirshkowitz et al., 2015, Kovacevic et al., 2018). It is reported that 1.8 million people have obstructive sleep apnoea in the United Kingdom (Carlos Rejon-Parrilla J, 2014, Mandavia et al., 2020). These sleep disorders have been associated with an increased risk of developing chronic health issues that

include hypertension, diabetes type 2, obesity, depression, and cancer (Altevogt and Colten, 2006, Kelley and Kelley, 2017). Additionally, sleep disorders can result in sleepiness during the day (Yaremchuk, 2018, Slater and Steier, 2012), can lead to less productivity at work, more prone to errors in judgement (Rosekind et al., 2010, Slater and Steier, 2012) and a significant risk to traffic accidents (Rosekind et al., 2010, Leger et al., 2012, Chaiard and Weaver, 2019).

There are pharmacological and non-pharmacological interventions for sleep disorders. Pharmacological interventions have statistically significant adverse events, including increased risk of falls and cognitive impairment (Glass et al., 2005, Reynolds and Adams, 2019). Exercise is a promising non-pharmacological treatment to enhance sleep. It is particularly appealing in a public health setting (Brady et al., 2009, Reynolds and Adams, 2019), including aerobic exercises (Edinger et al., 1993, King et al., 1997, Passos et al., 2010, Reid et al., 2010, Sharif et al., 2015, Guthrie et al., 2018, Bonardi et al., 2016) and strengthening exercises (Bonardi et al., 2016).

Our study showed no between-group or within-group improvement in sleep parameters when actigraphy data were compared. In fact, the intervention arm had shown a deterioration in onset latency ($P=0.015$) when compared between groups. In simple words, the data suggested that participants in the intervention group took a bit longer to sleep after getting into bed when compared to participants in the control group. In contrary to that, there was no between-group difference when the overall PSQI scores were compared. However, within group PSQI analysis showed that participants in the intervention group reported that they improved the quality of their sleep ($P<0.01$), the percentage

of time in bed that one sleeps (P=0.05) and improved sleep disturbance (P<0.01).

Most recent systematic analysis and meta-analysis reported that exercise improves selected sleep outcomes in adults, including apnoea-hypopnea index (AHI), overall sleep quality, global score, subjective sleep, and sleep latency (Kelley and Kelley, 2017), although the quality of evidence ranged from very low to low. Only three meta-analyses (representing 950 adults) fulfilled the inclusion criteria, and randomised controlled trials in these meta-analyses relied on subjective data and did not use actigraphy. They reported a small effect size and limited to a narrowly defined population, which is one of the limitations of their research. Our research findings partially agreed with this study, where participants in the exercise group reported improved subjective sleep quality and efficiency. Still, no improvement was observed on objective parameters.

Another systematic review studying the acute and chronic effects of resistance training on sleep quality and quantity reported that chronic resistance training exercise improved all aspects of sleep with the most significant benefit to sleep quality (Kovacevic et al., 2018). This was the first study that studied acute and chronic effects of resistance exercise and reported moderate to large improvement in sleep quality and minimal effects observed on sleep quantity. They used more than 4 bouts of exercise as ‘chronic’ effect of exercise. This study highlighted the fact that there is a lack of studies on acute resistance training and sleep (only one study performed in individuals with reported sleep disturbances). Additionally, none of seven studies on chronic resistance training included in this systematic review used objective assessment. This

emphasises that iBEAT-OA RCT is unique and assessed the chronic effects of exercises (bouts of 10 or more in exercise regimen) on sleep with subjective (PSQI questionnaire) and objective evaluation (actigraphy).

The sleep time in iBEAT-OA RCT was less than 4 hours in both arms at baseline and follow-up, whereas earlier studies have suggested 7-9 hours of total sleep time (Thurman et al., 2018, Fekedulegn et al., 2020). A study including participants with knee OA has reported a total sleep time of 4.96 hours (Campbell et al., 2015). Still, there is nearly a difference of approximately two hours reduced total sleep time in our cohort. As discussed in chapter 4, this parameter was not captured appropriately potentially due to a technical issue (discussed with manufacturers), and hence, this is one of the limitations of our study.

When variables such as Onset latency, WASO and sleep efficiency are compared to earlier studies (Table 4-3), the data falls within normal ranges. In my study, I found worsening onset latency in the intervention group compared to the control group but no difference in sleep efficiency and marginal improvement in WASO (not statistically significant, though). I will discuss these changes briefly.

The effects of exercise on sleep are influenced by factors such as exercise protocol and individual characteristics, including gender, age, BMI, fitness level and type of sleeper (Chennaoui et al., 2015). The exercise protocol may include acute or chronic exercise (short term versus long term exercise), aerobics or anaerobic and other factors such as duration, intensity, and weather (Chennaoui et al., 2015). Two meta-analyses looked into the effect of

acute exercise on sleep and reported improved onset latency and wakefulness occurring after defined sleep onset (WASO) when exercises were performed 4-8 hours before bedtime (Kubitz et al., 1996, Youngstedt et al., 1997). In comparison, this study did not restrict individuals to perform the exercise at a specific time, and they performed exercise as per their convenience. We observed a marginal increase (deterioration) in onset latency (0.01h) in the intervention group at follow-up. One potential explanation could be that some individuals performed their daily exercises at the end of the day (and not 4-8 hours before bedtime, as referenced above), thus affecting the onset latency of the intervention arm at follow-up. Comparing onset latency demonstrated by our study (ranges 0.02-0.03 hour in both groups at baseline and follow-up) to previous studies, the participants in our cohort had relatively short onset latency time compared to previously reported 0.24 hour by a study recruiting participants with knee OA (Campbell et al., 2015).

Comparing wakefulness occurring after defined sleep onset (WASO) in the intervention arm, it was marginally reduced (-0.01hour) at follow-up, which meant that sleep defragmentation improved in the intervention arm, albeit not statistically. WASO observed in our study is relatively less than 2.05 hours reported by earlier mentioned study with knee OA participants (Campbell et al., 2015).

Lastly, sleep efficiency in both arms deteriorated marginally, 3% in the intervention arm and 1% in the control arm at follow-up, indicating that the exercise arm had relatively more deterioration in their sleep efficiency. Comparing the data of our study to previous studies done on knee OA participants, 77% sleep efficiency of the intervention group at follow-up was

still better than 66% sleep efficiency reported by another study using actigraphy (Campbell et al., 2015).

There may be other reasons and limitations when assessing sleeping traits with actigraphy, and I will discuss them below.

Previous studies have shown that exercise affects sleep and sleep affect the ability to exercise (Chennaoui et al., 2015). Firstly and foremostly, most studies on exercise and sleep have targeted healthy young sleepers (<35 years) (Kubitz et al., 1996, Youngstedt, 2005, Youngstedt et al., 1997) and studies on elderly and poor sleepers using polysomnography (PSG) are limited and of poor quality (Youngstedt, 2005, Youngstedt, 2003), which is the limitation when I give reference to most studies on sleep and exercise.

The aerobic exercises have shown improvement in the quality and quantity of sleep (Edinger et al., 1993, King et al., 1997, Passos et al., 2010, Reid et al., 2010, Sharif et al., 2015, Guthrie et al., 2018, Bonardi et al., 2016). Similarly, resistance exercises have been shown to improve depression and cardiovascular disease (Singh et al., 1997, Williams et al., 2007) and sleeping disorders (Bonardi et al., 2016). The exercises used in this study cannot be classed as aerobics and fall more under resistance training, where participants used their body weight to train their muscles. Bonardi et al. (2016) compared the benefits of aerobic and combined aerobics and resistance training on sleep using actigraphy for ten consecutive weeks, exercising three times per week. They reported that aerobics are more helpful in improving sleep fragmentation and sleep quality when compared to combined aerobics and resistance training. The exception was sleep efficacy, which was better in the combined

exercise group. In comparison to their study, iBEAT-OA RCT used strengthening exercises. This might be a potential reason that this RCT did not see any objective improvement in sleep parameters. This intervention improved pain in the intervention group and not sleep, indicating that the strengthening exercises used in this RCT might be helpful to reduce pain but not sleep parameters.

Reviewing the literature in the older population with sleep disturbances, the pooled analysis indicated that exercise training has a moderate beneficial effect on sleep quality, onset latency and medication usage (Irwin et al., 2008, Yang et al., 2012, Buman et al., 2011). Only 3 out of 23 behavioural intervention trials reviewed by these authors had used objective measurements such as polysomnography (PSG). These studies indicated that a long term training exercise was needed to observe an effect of exercise improving sleep when assessed objectively (PSG), and improvement in sleep quality was observed after a 12-month exercise program (Irwin et al., 2008, Yang et al., 2012). In comparison, our trial assessed participants for six weeks only and a potential reason or limitation as to why our study did not observe a difference in sleep objectively (actigraphy).

The validity of actigraphy can get compromised due to inconsistency across studies related to the algorithms and methods used to identify sleep onset and sleep offset, marking the sleep region or total sleep time (Fekedulegn et al., 2020). One example is that some algorithms depend on the raw wrist movement values (Sitnick et al., 2008, Natale et al., 2014), while others use sleep/wake scores (Tranah et al., 2010, de Souza et al., 2003) to identify sleep region. Another example is defining the criteria of sleep latency, which includes

the interval from bedtime to first occurrence of 10 minutes block with at least 9 minutes of no movement, or the time elapsed from lights out to occurrence of five consecutive sleep minutes, or the interval from bedtime to the first occurrence of at least three successive minutes with no activity or the interval from bedtime to start of the first 20-min sleep block with greater than 19 min of sleep and this varies across actigraphy devices (Fekedulegn et al., 2020). Reviewing the technical data of our actigraphy, the method to assess the onset of sleep was not defined in their manual. Additionally, as mentioned earlier, time in bed and total sleep time parameters were not recorded appropriately and fell outside of normative values. This is another limitation of this study.

Although actigraphy data have been concordant with PSG (gold standard), the ability to detect sleep is substantially reduced in patients with disturbed sleep, specifically those who have frequent arousals and reduced total sleep time (Martin and Hakim, 2011). A previous study compared four groups; normal healthy individuals, non-arthritic participants with insomnia, participants with knee OA but without insomnia and participants with knee OA and insomnia (combined comorbidity group), and reported that the largest within-night differences between objective and subjective sleep measures were observed primarily in the knee OA group (Campbell et al., 2015). They reported that their cohort of knee OA had 21% worse observed sleep efficiency on actigraphy when compared to personal diaries, 108 minutes reduced total sleep time on actigraphy compared to personal diaries and 102 minutes of over-reporting WASO on actigraphy when compared to personal diaries. They implied that actigraphy data undermined many sleeping parameters when compared to personal sleep diaries. As iBEAT-OA RCT included participants with knee OA

as well, this might be one potential reason that this study observed very low total sleep time (3.8-3.86 hours) in both groups, thus having a significant difference compared to 7-9 hours of normative values for total sleep time (Fekedulegn et al., 2020). Reflecting hindsight, I think that I should have included sleep diaries as well.

Compared to objective measures, when subjective measures such as PSQI are reviewed, only 16 weeks of moderate-intensity exercise was required to improve the global PSQI score (King et al., 1997). I studied the benefit of exercise on sleep for six weeks only, and although I did not see improvement on total self-reported PSQI score however with-in group analysis showed that participants in the intervention group reported improvement in the quality of their sleep, the percentage of time in bed that one sleeps and improved sleep disturbances. This was achieved after six weeks of exercise intervention in our study.

Previous studies compared PSQI and parameters from actigraphy data, including older population (Beaudreau et al., 2012, Spira et al., 2011) and healthy younger and older adults (Grandner et al., 2006) reported a weak correlation coefficient between PSQI and actigraphy data. Our study had shown similar discordance between actigraphy data and the outcome of PSQI. The onset latency deteriorated in the intervention arm when actigraphy data were evaluated. In contrast, three questions on self-reported PSQI showed that the intervention group felt improving sleep quality, sleep efficiency and reduced sleep disturbances post-intervention.

There is a known association between sleep disturbances and chronic pain. Epidemiological (Wilcox et al., 2000, Power et al., 2005, Smith et al., 2009a) and experimental studies (Campbell et al., 2015, Harrison et al., 2003, Doherty and Smith, 1993, Leigh et al., 1988) have established a link between poor sleep and painful knee due to OA. Sleep disturbances can be due to pain as a result of chronic conditions such as knee OA, or due to central sensitisation (which may develop as a result of knee OA or other chronic comorbidities) or a combination of knee OA and central sensitisation (Campbell et al., 2015). In order to improve sleep, the focus should be on exercises, which should address pain as a result of knee OA as well as central pathways to reduce central sensitisation. The types of exercise used to relieve pain essentially focus on increasing muscle strength more than cardiovascular fitness (Rooks et al., 2002, Çolak et al., 2017). There is limited evidence on the efficacy of types of exercises that reduce central sensitisation (De Oliveira Silva et al., 2018). The observation that increases in muscle strength reduce clinical pain but not measures of central sensitization is consistent with previous reports linking the effect of chronic pain on sleep (Stocks et al., 2018) to central sensitisation. The type of exercise programme carried out in this RCT is clearly effective in relieving pain but appears not to significantly affect central modulation of pain, suggesting that other interventions are needed.

Sleep disturbances are often observed in depressive patients, and impaired sleep is, in many cases, the main complaint of depression (Fang et al., 2019, Steiger and Pawlowski, 2019). Although the underlying pathophysiology of this relationship remains vague, depression and insomnia have a complex bidirectional relationship (Fang et al., 2019, Gebara et al., 2018). This

relationship becomes further complex when OA is added as a third pathology, and I struggled to find relevant literature to address these three comorbidities with just exercise. There is ample evidence in favour of treating insomnia with cognitive behaviour therapy, relaxation therapy, deep brain stimulation and pharmacological intervention (Gebara et al., 2018), which ultimately helps with depression, however evidence focusing on exercise as a solo management plan is scarce. This RCT did not consider depression in our participants. Therefore, the discussion of depression, sleep and osteoarthritis may not benefit this thesis further, especially when there is not much literature on the efficacy of exercise alone, improving all these three factors as outcome measures.

The mechanism by which exercise alters sleep and whether benefits are mediated in part by physiological, psychological or neurobiological changes remain largely unknown (Uchida et al., 2012, Kovacevic et al., 2018). Exercise could potentially affect sleep by reducing pain (So et al., 2021, Chennaoui et al., 2015), improving sleep by improved symptoms of anxiety and depression (Fang et al., 2019), or altering energy expenditures such as increased body temperature (Hibi et al., 2017, McHill and Wright Jr, 2017). Future studies should factor in intervention length (acute/chronic), compare different interventions (resistance, aerobics, mind-relaxation) and answer the mediation factor of improved sleep with exercise intervention.

6.10 iBEAT-OA and Sonographic features of OA

A previous systematic review and meta-analysis reported no difference in synovitis or effusion in sufferers of knee OA post-exercise for six months and assessed on MRI scans (Van Ginckel et al., 2019). Similarly, iBEAT-OA RCT did not show any difference in sonographic features of knee OA pre and post-intervention between groups or within the intervention group. There may be multiple reasons for this. First and foremost, this may be attributed to the lack of significant inflammation in OA compared to rheumatoid arthritis, where these changes are marked (Hussain et al., 2018, Abramson and Attur, 2009). Secondly, this study was not powered to detect a statistical difference between sonographic features, as the sonographic examination was one of the secondary outcome measures. Additionally, only a small number of participants had a positive effusion. These low numbers reduced the statistical power, and hence there was a lack of statistically significant differences between the two groups.

6.11 Adverse Events

There were no serious adverse events reported with these exercises. This exercise programme has been trialled on seventy-five thousand patients from 2008 to 2015, with no serious adverse events reported (Thorstensson et al., 2015). There is a slight chance of an increase in knee, hip or back pain (Fransen et al., 2015) with most exercises. One participant in the intervention arm reported increased ongoing chronic low back pain and did not wish to

continue. This was recorded as an adverse event as per local guidelines, and the GP of this participant was informed in writing.

Another participant in the control group reported a drop in blood pressure and dizziness after the baseline assessment visit to Academic Rheumatology, City Hospital Nottingham. This participant suffered with stable angina and was on bisoprolol. The participant reported feeling dizzy after reaching home and was admitted to the hospital. It was established that this participant required a lower dose of bisoprolol, and the medication was adjusted. The participant dropped out of the study due to an unpleasant experience and ending up in an Accident and Emergency. As this participant was not in intervention arm, this adverse event could not be related to exercises. As per local guidelines, I registered it as an adverse event, and the participant's GP was notified in writing.

6.12 Adherence

The participants' compliance is usually greater with face-to-face sessions, and doing exercises in the home environment has been a challenge for most participants. This may be due to lack of motivation or self-discipline when patients are on their own. The mean (SD) adherence of the intervention group in this study was 87.9% (SD 14.3) by all participants based on the fact that they were supposed to exercise daily. A previous systematic review and meta-analysis reported 50-70% compliance for home-based exercise sessions (Chaabene et al., 2021) and our study had exceeded those numbers. There were 41 participants (85.4%) whose compliance was above 70%, and two participants with below 50% compliance to daily sessions.

During the intervention, three participants were contacted by SG due to missing four consecutive sessions. One participant reported increased low back pain (discussed in adverse events) and dropped out of this study. The second participant said some family commitments changed, and this participant wished to leave this study. The third participant was away on holiday; however, on contacting, this participant agreed to resume the exercise programme on return.

Additionally, four participants contacted SG due to various reasons. Most of these participants wanted reassurance as knee pain increased in the first 1-3 weeks after starting the intervention. After discussions and reassurance by SG, they resumed the exercise programme, which might have helped with the compliance. One participant missed 11 consecutive sessions due to tragedy in the family, which might have reduced the overall compliance. This facility of online chatting and discussing issues with a dedicated physiotherapist indeed helped the adherence rate. Other potential factors might be daily reminders sent via e-mail and potentially interesting educational sessions.

6.13 Strengths of this Study

This study has various strengths:

1- This study recruited participants with clinically and radiographically features of knee OA. I wanted to recruit only participants whose radiographs showed knee OA instead of participants with any chronic knee pain. A previous study has documented that only 74-80% of

participants recruited with chronic knee pain had knee OA (Mecklenburg et al., 2018) based on American College of Rheumatology criteria for knee OA (Altman et al., 1986). This is relevant as recruiting participants with chronic knee pain could potentially reduce the statistical power of our calculations and if we want to generalise our results on the sufferers of knee OA.

2- This study is a randomized control trial that had a control arm.
3- The research team gave a tablet to those participants who did not own a tablet.
4- A qualified senior physiotherapist carried out all the assessments.
5- This study used physical tests (30CST/ TUAG, muscle strength testing on a dynamometer) and QST to assess functions and pain instead of self-reporting assessments only.
6- This study used musculoskeletal ultrasound to assess knee joint and inflammatory signs of OA.
7- The improvement on subjective assessment (WOMAC and NRS) were backed up by the progress shown on objective measures (Muscle strength gains and functional improvement).
8- The compliance of the intervention group was 87.9% which exceeded 76 – 77% compliance rate for home-based exercise sessions (Messier et al., 2007, Wong et al., 2005).
9- MCID for NRS, TUAG, 30CST and WOMAC physical function exceeded their thresholds as explained under sections 6.3, 6.6 and 6.8 of this chapter. This corresponded to large to very large effect size, as described earlier.

10- By using a randomised controlled design, the study avoids the issue of regression to the mean (RTM). RTM is a statistical phenomenon that can make natural variation in repeated data look like real change, which takes place when unusually large or small measurements tend to be followed by measurements that are closer to the mean (Barnett et al., 2004). Because individuals were placed into each group randomly, therefore we minimised the chances of regression to mean at group level.

6.14 Limitations of this study

There are multiple limitations of this study.

1- This study showed pain improvement on self-reported pain scores (NRS), a subjective assessment tool. This study failed to show an improvement in objective assessment (QST) over six weeks.
2- COVID-19 lockdown ruled out the planned follow-up face-to-face visit in 27 participants, preventing the study from reaching the planned statistical power. Five additional participants discontinued treatment, but this loss to follow-up was less than the expected loss of 10-12%. However, the number of participants that did not attend the 6-week follow-up were similar in both groups, had similar demographics and baseline characteristics compared with the analysed set of participants (Chapter 3, section 3.7).
3- Initially, I had decided to analyse the outcomes using the intention to treat (ITT) approach. However, as I was forced to stop the study early

because of the UK going into lockdown in March 2020 and was unable to perform a follow-up visit on a subset of enrolled participants for reasons beyond my control, the analysis might be better described as “per protocol” (PP) under such circumstances. Both ITT and PP analyses are valid, with the first one assessing the effect of assigning a treatment with PP analysis, researchers investigate the effect of receiving the assigned treatment, as specified in the protocol (Tripepi et al., 2020). I did compare; however, the baseline characteristics of individuals not completing the study either due to lockdown or drop-out for other reasons and found no significant difference between those completing the study and those dropping out (Chapter 3, section 3.7). Therefore, this factor is unlikely to have introduced bias to the analysis or conclusions of my study. Despite this, per-protocol analyses might have exaggerated the treatment effect (Ranganathan et al., 2016), which might be a limitation of this study.

4- Blinding was not possible for this study, and potential placebo effects associated with digital care compared to care-as-usual treatment are not accounted for. This study could not rule out some confounding factors such as proprioception for functional assessments and depression. The education level and socioeconomic status of the participants were not considered and assessed as confounding factors.

5- This RCT showed an improvement of 1.8 units in the primary outcome (NRS) in the intervention arm compared to 0.3 unit improvement in the control group. The control group was treated in accordance with the current standard of care to manage OA. Nevertheless, the

improvement in the control and intervention groups, lack of blinding and considering that this RCT lasted six weeks (short term intervention with assessments done twice), I could not rule out the Hawthorne effect as a potential explanation for the improvement observed. The Hawthorne effect refers to a change in behaviour as a motivational response to the interest, care, or attention received through observation and assessment (Sedgwick and Greenwood, 2015). This is a potential study limitation with regards to pain and other patient-reported outcomes, but it is unlikely that the Hawthorne effect may have resulted in the objective improvements in muscle strength and function observed in the intervention group. Moreover, exercise has been repeatedly shown to be effective at relieving pain and is part of the current guidelines making it unlikely that the improvements in pain seen in the treatment arm can be attributed solely to the Hawthorne effect.

6- Both groups were obese (mean BMI of control group = 31.9, mean BMI of intervention group = 30.4). 64% of adults in England are overweight or obese, according to figures collected from health survey England (Centre, 2019), and Nottingham has been reported as one of the worst cities in England for obesity-related hospital admissions (Pritchard, 2019). Unfortunately, this was unavoidable while the study was conducted in Nottingham; however, baseline characteristics for both groups were same at baseline without any statistical difference.

7- The factors leading to the superiority of the digital programme over routine self-management in the present study are not apparent. It is

possible that daily delivery of individualised treatment, together with support, engagement and support from healthcare professionals, may have played a role (Dahlberg et al., 2020, Nero et al., 2017, Cronström et al., 2019a). Other studies suggest that increasing exercise frequency, but not necessarily length of sessions, can improve pain relief and that exercise should be performed at least three times a week (Juhl et al., 2014, Polaski et al., 2019).

8- This study used the MSK-HQ questionnaire to look at multiple factors including pain, stiffness, sleep and quality of life to cover broad aspects of knee OA. Although using MSK-HQ questionnaire can be interpreted as a strength of this study, participants should improve on all these factors to show a difference in MSK-HQ score. This in itself is the weakness of this questionnaire and a potential reason that I did not see improvement on MSK-HQ while functions such as 30CST, TUAG (objective assessments), and WOMAC score (subjective assessment) improved.

9- Our study collected participants' subjective and objective data over six weeks only; therefore, this study observed the ‘short term’ benefits of exercise on sleep. Previous studies reported improved sleep quality after a 12-month exercise program (Irwin et al., 2008, Yang et al., 2012) when assessed objectively (PSG). This might be one limitation of our study as to why I could not establish any improvement in objective sleep parameters. Additionally, as mentioned earlier, time in bed and total sleep time parameters were not recorded appropriately and fell outside of normative values, indicating another limitation for sleep parameters

in this study. Nevertheless, the participants in the exercise group reported improved sleep quality and efficiency with reduced sleep disturbances on the PSQI questionnaire.

10- The study used block randomisation to address logistic issues linked to the use of tablets for participants without a smartphone. Although this would not have biased our sample size had the study not been forced to stop, the early termination of the study due to lockdown in March 2020 meant that this method of randomisation resulted in a higher number of control than intervention arm participants.

11- Lastly, this study has assessed the benefit of exercising for six weeks. Further studies are required to establish the long-term benefits of digital intervention and evaluate the ceiling effect. Caution should be used in extrapolating our findings beyond the six weeks.

6.15 Impact of this study

The World Health Organization declared a COVID-19 pandemic on 11th March 2020, and there has been discussion around 'prolonged or intermittent social distancing' until 2022 (Kissler et al., 2020). Accessing information on health and diseases were already being used by people living with chronic conditions (Gagnon and Sabus, 2015, Fox S, 2013); however COVID-19 pandemic has highlighted the importance of using digital health during this pandemic (Haider et al., 2020). This pandemic has presented an unprecedented challenge for health services globally (Smith et al., 2020), including national health services (NHS), which have been pushed to its limits and modify the way the NHS

delivers care. In order to avoid spreading COVID-19, there is likely reduction in face to face exercise groups and physiotherapy during this pandemic to prevent spreading the virus, and there is an urgent need to utilise alternate methods such as digital health or telemedicine during the current pandemic (Haider et al., 2020). This pandemic has promoted and accelerated digital health and telemedicine (Webster, 2020). The timing of this study is ideal as the results are presented during this pandemic when health services and patients are looking for the provision of healthcare digitally. The results of our study have provided evidence that patients suffering from knee OA can be managed digitally and in their home environment safely.

Being the first study on digital health aimed specifically at knee OA in the UK, this study will encourage the development of digital interventions for other joints in the human body. It will promote the implementation of digital health services in the UK. This study will encourage further research on digital health and the development of digital health/apps, leading to a potential business plan providing musculoskeletal care digitally. As a result, if healthcare is delivered digitally, this will reduce the carbon footprint of travelling and time spent travelling to clinics, thus saving patients' time and making this planet relatively eco-friendly.

Our study has established that digitally delivered exercises reduce pain and improve the functional abilities of patients. This study has shown a significant correlation between reduced TUAG scores and improved muscles strength of quadriceps and hamstring. The improvement in TUAG is only correlated with strength gains of quadriceps and hamstring muscles but not with the pain reduction, thus highlighting the importance of strengthening muscles relatively

more than reducing pain around the knee joint to improve functional abilities. This is considered a scientific advancement where I have answered a few unanswered questions.

To summarise, our study will promote digital health and patients' safety by doing exercises in the home environment, potential business plans, scientific advancement, further research, cost-effectiveness, and eco-friendly aspects of digital health.

6.16 Conclusion

This study showed that a digitally delivered first-line knee OA management programme (iBEAT-OA) was superior to self-managed care when the primary outcome pain and secondary outcomes of function performance and muscle strength were compared.

The reduction in pain and improvements in function seen through exercise do not correspond to reductions in pain sensitivity or measures of central sensitisation, synovitis, or sleep. Although all these factors may influence the pain experience in OA, they do not appear to be influenced by muscle strengthening exercises.

To summarise, the present study suggests that digital treatment for knee OA is an effective way of managing knee pain, improving muscle strength and functional improvements. This exercise program has the potential to decrease the OA burden on both the health care systems and patients.

6.17 Recommendations for Future Research

Future research may investigate the minimum duration required for web-based exercises to effectively reduce knee pain and equally at which point we see a plateau in the improvements. Further work can be directed toward exploring the intervention's underlying mechanism for reducing pain and improving functions. Additionally, further research is needed to confirm these findings in the long term and investigate the dose-response relationship between muscle strength gains and improvement in physical functions. When considering sleep as a factor along with exercises and knee pain, future studies should factor in intervention length (acute/chronic) and answer the mediation factor of improved sleep with exercise intervention.

This study has collected biomarkers (bloods, faecal samples and synovial fluid). Further work can be carried out to see any changes in the exercising arm's biomarkers compared to the control arm. There is currently some work planned which is due to start with the local hospital to assess biomarkers. Additionally, synovial fluids collected during this RCT will be studied in collaboration with Oxford University. There is an idea of setting up the first UK based biobank collecting and evaluating synovial fluids.

Another future direction would be to assess the cost-effectiveness of this digital intervention in the UK. In fact, as of result of this RCT, there is some work going on in London where different GP surgeries are trialling the JA app as the first line of treatment for knee and hip OA patients. This new project aims to establish the cost-effectiveness and feasibility of this app in the UK. If the

results of this project are promising, then the future direction will be to assess and withstanding acceptability within NHS as pathways for knee OA treatment.

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Appendix 1

Participant information sheet (PIS)

Consent form

Ethical Approval Letter

KNEE OSTEOARTHRITIS AND WEB-BASED EXERCISES

PARTICIPANT INFORMATION SHEET

Chief Investigator: Dr Ana Valdes, Associate Professor and Reader in Musculoskeletal Genetics

We would like to invite you to take part in our research study. Before you decide, it is essential for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like further information. Take time to decide whether you want to take part.

What is the purpose of the study?
Knee pain due to osteoarthritis (OA) is a leading cause of pain and reduced mobility in adults over the age of 50. Although certain risk factors for the development of osteoarthritis (e.g. getting older, genetic makeup) are known, it is still unclear why some people with OA develop progressively severe pain, while others with a similar amount of OA change have a mild or even no pain.

The purpose of this study is to test a web based exercise intervention to reduce osteoarthritis pain, and in addition, to try and determine the effect of exercises on the level of pain which you routinely experience and on the quality of your sleep. We anticipate that these exercises will reduce your pain levels and improve your sleeping habits, thus potentially reducing the progression of osteoarthritis. If this study proves that these exercises are effective, then our recommendations will be to offer these exercises as routine management to patients suffering from knee osteoarthritis.

Individuals with mild to severe knee pain are being invited to participate in the study to enable comparisons to be made between the different categories of knee pain and to identify features that may help explain the differences in pain severity between individuals.

Why have I been invited?
You have already very kindly completed and participated in our previous studies (Knee pain in the community), and hence we are contacting you to see if you are interested in this study.

OR

We are sending you this information sheet as our research team has identified that you suffer from knee arthritis and hence this information sheet is sent to you.
You should read this information sheet in detail before deciding whether you wish to take part or not. We aim to recruit 140 individuals for this study.

Do I have to take part?
No. You should only take part in this study if you want to. It is entirely up to you whether or not you wish to take part. If you do, we will ask you to sign a consent form. We will X-ray your knee (s) to see if you qualify for this study. This will not be

necessary if you have already had X-rays in last 12 months showing that you have knee arthritis. Once we establish that you are eligible to participate in this study based on the x-rays of your knee, we will proceed with the rest of the assessment. If your x-ray indicates you are not eligible, you will be withdrawn from the study. You are free to withdraw at any time, without having to give a reason. This in no way will influence the medical care you receive from your GP or local hospital, or in any way affect your legal rights.

What will happen to me if I take part?

The study that we are inviting you to join is looking at the benefits of internet-based exercises on pain, quality of sleep, strength of muscles around your knees and overall quality of life. On a random basis, you will be allocated to either an exercise group or a control group.

Both groups will go through the assessment, however, there will be no exercises recommended for the control group, and you will follow the plan or exercises given by GP or instructions recommended by research UK arthritis.

If you are allocated to the exercises group you will get login details via e-mail so that you can enrol in the online knee exercise academy (the Joint Academy) and start doing the exercises for your knee pain. You will be asked to complete background information online, following which a tailored exercise and the educational programme will be created for you. You will then be expected to log in daily and complete that day's activity, which will be designed to take 5 – 30 minutes a day. You will also have contact details for a member of the research team if you have any problems with the programme. The research team at Nottingham will have access to your data recorded by the Joint Academy. We will encourage you to participate in these sessions regularly.

If you are allocated to the control group you will not be given access to the Joint Academy during your first visit but you will be asked if you wish to do the exercises after your second visit and if you do express such desire, you will be given login details so that you can do the 6-weeks exercise programme.

Regardless of the group that you are assigned to you will be invited to take part in two hospital visits planned over the period of 6-8 weeks apart. A range of assessments will be undertaken at an initial hospital appointment and will then be repeated approximately six to eight weeks later. The assessments include an X-ray of your most painful knee (only during the first visit and only if you have not had an X-ray performed in past 12 months), tests to measure muscle strength, measures of your pain sensitivity, an ultrasound scan of your knee and collection of blood, faeces and urine samples to measure chemical changes which associate pain to osteoarthritis. Also, if you are agreeable, an aspiration of knee fluid will be conducted which will help us to examine certain changes in the water in your knee to understand the relationship between pain and osteoarthritis. These examinations will be repeated 6-8 weeks later to determine if doing specific exercises make any difference to attributes mentioned above when compared to the group who don't do the exercises.

If you inform us that you are happy to take part in this study, you will be contacted by the research team to arrange a single morning appointment to attend the Nottingham City Hospital to see a research nurse.

This initial appointment will take around 3 hours. You will be given the opportunity to ask any questions you have about the study before being asked to sign a consent form. You will then be given a self-reported questionnaire to complete on your

physical activity, knee pain and overall well-being. The following assessments will then be undertaken:

- **Fasting blood and urine sample collection**

You will be asked to have nothing to eat after 10 pm from the night before your appointment so that you can provide fasting blood and urine samples when you attend for your appointment. You can drink water during this fasting period.
Further details concerning the collection of the urine sample will be confirmed when you are contacted by the research team, and a summary of the information will be sent to you with the confirmation of your appointment. The research nurse will take a sample of 10 ml of blood (2 tablespoons) from a vein in your arm. We will then provide you with a light, refreshing breakfast and a hot drink.

- **Functional Tests**

You will be asked to stand from a chair and walk 3 metres. You will have to walk back to your chair and then sit. It will be timed. We will also assess the number of times you can stand from a chair in 30 seconds. We will use standardised functional measures to assess your physical functioning.

- **Muscle Strength**

The strength of your knee muscles will be tested using a machine. You will sit on a chair which will be connected to a machine with a lever arm. A research nurse/physiotherapist will explain the procedure to you. You will be given a chance to try it without taking any readings. Once you are confident that you understood the procedure, we will ask you to push a lever arm on the machine using the thigh muscles which will help us to establish the strength of knee muscles at that time.

- **Ultrasound:**

An ultrasound machine will be used to image your most painful knee joint for any underlying inflammation or swelling. This scan is a non-invasive procedure; it does not involve any exposure to ionising radiation and has no detrimental side effects. Similarly, a measurement of the thickness of one of your thigh muscles will be taken. If you agree to have fluid extracted from your knee a needle will be inserted around the knee under the guidance of ultrasound. Therefore it can reach the targeted fluid safely without giving you much pain. A small amount of fluid will be extracted. The pain encountered during this procedure is similar to what you get while having an injection.

- **Pain Sensitivity measures (Quantitative Sensory Testing - QST)**

We will also measure how sensitive your nerves are to changes in mechanical pressure or sharpness. Pressure sensitivity is tested by using a probe to apply pressure to specific sites including your knee, shin and the side of your elbow. To test for sensitivity to sharpness, a "pinprick" stimulator will be applied to your skin, and you will be asked to rate the pain or sharpness you experience on a given scale. The simulator will be applied to your knee for less than a second each time. The "pinprick" stimulators are designed not to puncture your skin, and the devices are always disinfected before application. So that you know what to expect, the researcher will demonstrate the tests on one of your hands or your other knee. Any sensation of pain or pressure will be mild and temporary.

- **X-rays of your knees**

You will also be asked to visit the X-ray Department at the Nottingham City Hospital to have x-rays of your painful knee but only during the first visit. It will be done ONLY if you have not had knee x-rays in last 12 months.

- **Assessment of sleeping habits**

People with chronic pain often suffer from difficulties with sleep. Your sleeping pattern will be collected using a wearable device similar to a watch called an actigraph. We will give you a wearable device which should be worn on your wrist for 6-8 weeks. We will collect this device on the next face to face session. You will be given instructions on how to charge this device if needed.

- **Stool sample**

The microbes in our gut have been shown to affect inflammation and pain, so you will be given the option to donate a faecal sample. If you are willing, you will be given a collection kit with instructions during the first appointment for you to collect the stool at home and ship it back to us by post.

What are the possible disadvantages and risks of participating in this study?

X-raying your knees involves exposure to a tiny amount of additional radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation. The x-rays from this trial have been estimated to be roughly equivalent to half a day of background radiation in the UK. At this dose level, no harmful effects of radiation have been demonstrated, and the risk is believed to be minimal.

During the Pain sensitivity assessment (QST) you may feel a slight discomfort in the area the probe is placed, but this is only temporary feeling.

The blood tests may cause you some mild discomfort and occasionally a small bruise. If you agreed to ultrasound-guided knee aspiration, then it will cause you mild discomfort similar to blood extraction and occasionally a small bruise.

These exercises are very safe, and have been tested in over 70000 patients in the past 10 years. There is a small chance that it may increase your knee, hip or low back pain. This usually happens by using those muscles, which you may not have used for past few months or years. These pains settle themselves within few days. We will monitor your pain levels on a weekly basis, and any unexpected and non-resolving pains will be taken seriously. You will be advised to stop the exercises and contact your GP, should this happen.

Although it has not been previously reported for the current type of exercises, there is also a very small chance that your blood pressure could raise for short periods. If you encounter severe headaches, confusion, vision problems, chest pain, difficulty breathing, irregular heartbeat, blood in urine or pounding in your chest, neck or ears, you should STOP the exercises immediately. You are advised to contact your GP as soon as possible in such instances and inform us. If you wish to read more on high blood pressure, then it can be found on NHS Choices website, which is:

https://www.nhs.uk/conditions/high-blood-pressure-hypertension

What are the possible benefits of taking part in this study?

You will not benefit directly from participation in this study, but the results of this study may allow us to understand better the factors that cause different degrees of pain severity in people with knee pain. This may subsequently lead to better assessment and possibly better management of people with painful knees and OA.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to Dr Bonnie Millar (Research Coordinator) on 0115 823 1676.

If you remain unhappy and wish to complain formally, the Patient Advice and Liaison Service (PALS) provide a confidential service and can also advise you regarding the NHS complaints procedure – details are:

Free Phone:	0800 183 0204
Text phone:	07812 270 003
Email:	PALS@nus.nhs.uk
Online:	www.nuh.nhs.uk
Write:	NUH NHS Trust C/O PALS Freepost NEA 14614 Nottingham NG7 1BR

What will happen to any samples I give?
The blood, synovial fluid, faecal and urine samples will be stored securely with a code unique to you at the University of Nottingham. We would also like to seek your consent so that any remaining samples may be stored and used in possible future research- this is optional (please indicate you agree to this on the consent form). The samples will be stored with a code unique to you and secured at the University of Nottingham under the University's Human Tissue Research License (no 12265).
Some of these future studies may be carried out by researches other than a current team of Dr Valdes, who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in any way. If you do not agree to this, any remaining samples will be disposed of in accordance with the Human Tissue Authority's codes of practice.

Will any genetic tests be done?
No. There will be no genetic testing done during this study.

Will my taking part in the study be kept confidential?

We will follow the 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).

Your e-mail address, name and pain levels will be held online on the database of Joint Academy (Swedish Company). Their website is secure, however, it's your right to know that these details are held by them. These details will be kept secure for five years, however, if requested then these details can be deleted on the completion of this study.

The results of the study (averaging over all the participants) will be published in medical literature, but your identity will not be disclosed and all the analysis of data derived from the study will be done only using a number as an identifier and never with your name or date of birth in it.

Where possible information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it, however sometimes we need to ensure that we can recognise you to link the research data with your medical records so in these instances we will need to know your name and date of birth.

We will ask for your permission to store your personal details on a secure database within Academic Rheumatology to enable us to invite you to take part in future research studies. If this happens, you will be given the opportunity to decide whether you would like to take part or not. If you state that you do not wish to be contacted regarding future studies your personal details will be destroyed when the results of the study have been analysed.

X-rays will be stored electronically on the Nottingham University Hospital system (PACS). These images will be assessed at University site to assess the degree of arthritis on K/L scale.

All research data will be kept securely for seven years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with other Universities and researchers, including those in other countries. Sharing research data is important to allow peer scrutiny, re-use (therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information, we will seek your consent for this. You will be made aware then if the data is to be shared with countries whose data protection laws differ from those of the UK and how we will protect your confidentiality.

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.

Involvement of your General Practitioner/Family doctor (GP)
All the procedures outlined above are being carried out for research purposes only, and your GP will not be informed of your participation in the study. However, if x-rays raise any concerns, we will advise the participants to see their GP.

Will I be paid for participation in this study?
The study is entirely voluntary. You will receive no payment for your participation, however, all your travel costs to and from the City Hospital will be reimbursed.

What will happen to the results of the research study?
We hope that the results of this study will lead to a better understanding of the benefit of exercises and knee arthritis. 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 results if you wish.

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 study is being funded by the Arthritis Research UK (ARUK) Pain Centre and by the Musculoskeletal Ageing Research Centre funded jointly by ARUK and the Medical Research Centre (MRC) here at the University of Nottingham.

Who has reviewed the study?
This study has been reviewed by the East Midlands- Nottingham 1 Research Ethics Committee.

Further information and contact details:

Study Contacts: Dr Bonnie Millar, Research Coordinator, Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB Tel: 0115 823 1676

Chief Investigator: Dr Ana Valdes, Associate Professor and reader in Musculoskeletal Genetics, NIHR Nottingham Biomedical Research Centre, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB

Research Contacts:
Dr Bonnie Miller, Research Coordinator: Tel: 0115 823 1676

Thank you for taking the time to read this information sheet.

Nottingham Biomedical Research Centre

University of Nottingham UK | CHINA | MALAYSIA

ARTHRITIS RESEARCH UK

NHS National Institute for Health Research

KNEE OSTEOARTHRITIS AND WEB-BASED EXERCISES CONSENT FORM
(Principal Investigator: Dr Ana Valdes)

REC ref: 18021

Name of Researcher:

Name of Participant: **ID** ☐☐☐☐☐

	Please initial below
1. I confirm that I have read and understood the information sheet Final Version dated 06th July 2018 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. 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 my medical notes and 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 I understand that my personal details will be kept confidential. These details will be held secure by the research team for 07 years after the end of this study. After this time, my data will be disposed securely.	☐
4. I understand the cells in my blood and urine will be tested for biomarkers (blood components such as enzymes, hormones, proteins, lipids) that might identify risk or severity of osteoarthritis and changes associated with pain. I understand that samples taken for this study will be stored in the Clinical Sciences Building, Nottingham City Hospital. I know that I will not receive the results of the biomarker tests.	☐
5. I agree to take part in Pain Sensitivity Testing also known as Quantitative Sensory Testing (QST). (Refer to Pain sensitivity measures on Patient Information Sheet if you require more information on this).	☐
6. I understand that my data will be stored safely and securely in a database in a password encrypted format for 7 years from the end of this study.	☐

KNEE OSTEOARTHRITIS AND WEB-BASED EXERCISES CONSENT FORM
(Principal Investigator: Dr Ana Valdes)

Name of Participant: **ID** ☐☐☐☐☐

7. I agree that the samples I have given and the information gathered about me can be stored by the University of Nottingham in the Clinical Sciences Building for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team of researchers who ran the first study, including researches working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in any way.

Consent		Yes	No
Mandatory	Blood		
	Urine		
Optional	Faeces		
	Synovial Fluid- fluid taken from the knee joint		

8. I agree to participate in the above study. ☐

Name of Participant	Signature of Participant	Date
Name of researcher	Signature of researcher	Date

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Ana M Valdes
NIHR Nottingham Biomedical Research Centre, School of Medicine, University of Nottingham
Academic Rheumatology, Clinical Sciences Building,
City Hospital Nottingham
NG5 1PB

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

23 July 2018

Dear Dr Valdes

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Randomised controlled trial evaluating the efficacy of web-based exercises on knee pain due to knee osteoarthritis**
IRAS project ID:	**244266**
Protocol number:	**18021**
REC reference:	**18/EM/0154**
Sponsor	**University of Nottingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales*, as well as any documentation that has been updated as a result of the assessment.

*'In flight studies' which have already started an SSI (Site Specific Information) application for NHS organisations in Wales will continue to use this route. Until 10 June 2018, applications on either documentation will be accepted in Wales, but after this date all local information packs should be shared with NHS organisations in Wales using the Statement of Activities/Schedule of Events for non-commercial studies and template agreement/ Industry costing template for commercial studies.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of

capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Angela Shone
Tel: 01158467906
Email: sponsor@nottingham.ac.uk

Who should I contact for further information?

IRAS project ID	244266

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **244266**. Please quote this on all correspondence.

Yours sincerely

Chris Kitchen
Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Angela Shone, University of Nottingham (Sponsor Contact)*
Dr Maria Koufali, Nottingham University Hospital (R&D Contact)

IRAS project ID	244266

List of Documents

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		30 April 2018
GP/consultant information sheets or letters [GP flyer]	Final Version1.1	06 July 2018
HRA Schedule of Events [SoE for PICs]	1	06 June 2018
HRA Schedule of Events [SoE for City Hospital]	1	06 June 2018
HRA Statement of Activities [SoA for City Hospital]	1	07 June 2018
HRA Statement of Activities [SoA for PICs]	1	07 June 2018
Instructions for use of medical device		05 May 2018
IRAS Application Form [IRAS_Form_090718]		09 July 2018
Laboratory Manual		05 May 2018
Letter from funder [Arthritis Research UK funding letter]		08 October 2014
Letters of invitation to participant [Invitation letter]	Final Version1.0	26 April 2018
Other [Joint academy documentation]		05 May 2018
Other [QST elbow diagram]		05 May 2018
Other [QST knee diagram]		05 May 2018
Participant consent form [Participant consent form]	Final Version1.1	06 July 2018
Participant information sheet (PIS) [Participant information sheet]	Final Version1.1	06 July 2018
Research protocol or project proposal [Protocol]	Final Version1.1	06 July 2018
Summary CV for Chief Investigator (CI) [Dr Ana's CV]		26 April 2018
Summary CV for student [CV for Sameer Gohir PhD student]		26 April 2018
Summary CV for supervisor (student research) [CV of Dr Paul]		28 May 2018
Summary CV for supervisor (student research) [CV of Dr Abhishek]		28 May 2018
Validated questionnaire [MSK - HQ]		08 May 2018
Validated questionnaire [NRS]		08 May 2018
Validated questionnaire [WOMAC]		08 May 2018
Validated questionnaire [QST assessments]		08 May 2018
Validated questionnaire [TUAG and 30CST protocol]		08 May 2018
Validated questionnaire [Ultrasound and QST record sheet]		08 May 2018

IRAS project ID	244266

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	A University of Nottingham Non-Commercial Agreement, based on the model Non-Commercial Agreement (mNCA) will form the agreement of the NHS organisation to participate. Details of modifications made from the mNCA are provided in question 5 of the Statement of Activities.
4.2	Insurance/indemnity arrangements assessed	Yes	IRAS A77 states that no-fault compensation will not be offered. The applicant has confirmed that no-fault compensation will be offered.
4.3	Financial arrangements assessed	Yes	The study is funded via a centre grant from Arthritis Research UK.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any	Yes	The Ionising Radiation Medical

Section	Assessment Criteria	Compliant with Standards	Comments
	applicable laws or regulations		Exposure Regulations (IRMER) and the Human Tissue Act apply.
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a non-commercial study with two site types. A single secondary care site will act as a research site. GP practices in the CRN East Midlands geographical area will act as Participant Identification Centres. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

IRAS project ID	244266

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator is expected to be in place at the **research site**. Neither a Principal Investigator nor a Local Collaborator is expected to be in place at **Participant Identification Centres**. As per the Statement of Activities provided for both site types, the sponsor will not provide any training. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
No access arrangements are expected as all study activity at the participating NHS organisation will be undertaken by NHS staff who have a contractual relationship with the organisation.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix 2

Study questionnaires and forms for assessments

Web based exercises and knee OA

Participant ID _____ **Date**____ **Time** _____ **Study ID** _____

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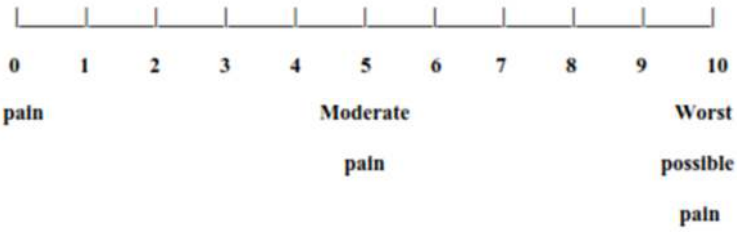
Numeric Pain Intensity Scale

Participants will be asked to rate their pain from 0 to 10, choosing the number that best represents the intensity of the pain they are experiencing. Generally, the pain in the 1–3 range is considered mild pain, 4–6 indicates moderate pain, and 7–10 is the highest level, or severe level, of pain.

There is no right or wrong number for patients to report. The researcher should ask the patient to rate the pain, and he or she should believe the number the patient reports.



Web based exercises and knee OA

Participant ID _____ Date____ Time _____ Study ID 244266

Bloods _____ Urine second void _____ Check meds _____ Weight kg _____ Height _____ K/L Score: _____

Ultrasound

Measure	Left Knee	Right Knee	Current Pain 0 -10
Effusion present (≥ 4mm)	mm	mm	
Synovial Hypertrophy (≥ 4mm)	mm	mm	Knee pain duration
Power Doppler Signal			

QST (KPa)

Most Painful Knee *(Demonstrate probe on Pts nail)*	Right / Left
A: Superolateral Patella 2cm	
B: Superomedial Patella 2cm	
C: Medial Joint Line 3cm	
D: Tibialis Anterior Muscle 5cm	

Temporal Summation Pin Prick (256mN)

Demo on back of Pts hand Most Painful Knee *(Bent leg. 5cm from centre Patella)*	Right / Left Test 1	Right / Left Test 2
Single measure		
Repeated measure		
TSP Score (R-S=)		

CPM (KPa)

Most Painful Knee *(Demonstrate probe on Pts nail)*	Right / Left		
Tibialis Anterior Muscle 5cm (U)			
Tibialis Anterior Muscle 5cm (C)		CPM score: (C-U)	

Time Up and Go Test

1		2		3		Average	

30CST score:

Web based exercises and knee OA

Participant ID _____ Date____ Time _____ Study ID 244266

K/L Score: _____

Ultrasound

Measure VL	Measurement 1	Measurement 2	Measurement 3
Fascicle length	mm	mm	mm
Fascicle Angle	Degrees	Degrees	Degrees
Muscle Thickness	mm		

Isokinetic Testing

Isokinetic Peak Torque	60° s−1	180° s−1
1st Attempt		
2nd Attempt		
3rd Attempt		
Highest Reading		

Pt ID _____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1_____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2_____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3_____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4_____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5_____
Component 6	#6 Score	C6_____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7_____

Add the seven component scores together _____ ***Global PSQI*** _____

A total score of "5" or greater is indicative of poor sleep quality.
If you scored "5" or more it is suggested that you discuss your sleep habits with a healthcare provider

Web based exercises and knee OA

Participant ID _____ Date____ Time _____ Study ID 244266

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WOMAC OSTEOARTHRITIS INDEX

1. **The following questions concern the amount of pain you are currently experiencing in your knees. For each situation, please enter the amount of pain you have experienced in the past 48 hours.**

		None	mild	moderate	severe	extreme
A. Walking on a flat surface	A.	☐	☐	☐	☐	☐
B. Going up or down stairs	B.	☐	☐	☐	☐	☐
C. At night while in bed	C.	☐	☐	☐	☐	☐
D. Sitting or lying	D.	☐	☐	☐	☐	☐
E. Standing upright	E.	☐	☐	☐	☐	☐

2. **Please describe the level of pain you have experienced in the past 48 hours for each one of your knees.**

	None	mild	moderate	severe	extreme
A. Right knee A.	☐	☐	☐	☐	☐
B. Left knee B.	☐	☐	☐	☐	☐

3. **How severe is your stiffness after first awakening in the morning?**

None	mild	moderate	severe	extreme
☐	☐	☐	☐	☐

4. **How severe is your stiffness after sitting, lying, or resting later in the day?**

None	mild	moderate	severe	extreme
☐	☐	☐	☐	☐

5. **The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the last 48 hours, in your knees.**

What degree of difficulty do you have with:

	None	mild	moderate	severe	extreme

Web based exercises and knee OA

Participant ID _____ Date____ Time _____ Study ID 244266

A. Descending (going down) stairs	A.	☐	☐	☐	☐	☐
B. Ascending (going up) stairs	B.	☐	☐	☐	☐	☐
C. Rising from sitting	C.	☐	☐	☐	☐	☐
D. Standing	D.	☐	☐	☐	☐	☐
E. Bending to floor	E.	☐	☐	☐	☐	☐
F. Walking on a flat surface	F.	☐	☐	☐	☐	☐
G. Getting in/out of car	G.	☐	☐	☐	☐	☐
H. Going shopping	H.	☐	☐	☐	☐	☐
I. Putting on socks/stockings	I.	☐	☐	☐	☐	☐
J. Rising from bed	J.	☐	☐	☐	☐	☐
K. Taking off socks/stockings	K.	☐	☐	☐	☐	☐
L. Lying in bed	L.	☐	☐	☐	☐	☐
M. Getting in/out of bath	M.	☐	☐	☐	☐	☐
N. Sitting	N.	☐	☐	☐	☐	☐
O. Getting on/off toile	O.	☐	☐	☐	☐	☐
P. Heavy domestic duties (mowing the lawn, lifting heavy grocery bags)	P.	☐	☐	☐	☐	☐
Q. Light domestic duties (such as tidying a room, dusting, cooking)	Q.					

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ParticipantID_____Date____Time_____StudyID 244266

Arthritis Research UK

NHS England

ARTHRITIS RESEARCH UK MUSCULOSKELETAL HEALTH QUESTIONNAIRE (MSK-HQ)

This questionnaire is about your **joint, back, neck and muscle symptoms** such as aches, pains and/or stiffness.

Please focus on the particular health problem(s) for which you sought treatment from this service.

*For each question **tick** (✓) **one box** to indicate which statement best describes you **over the last 2 weeks**.*

1. Pain/stiffness during the day How severe was your usual joint or muscle pain and/or stiffness overall **during the day** in the last 2 weeks?	Not at all ☐	Slightly ☐	Moderately ☐	Fairly severe ☐	Very severe ☐
2. Pain/stiffness at night How severe was your usual joint or muscle pain and/or stiffness overall **at night** in the last 2 weeks?	Not at all ☐	Slightly ☐	Moderately ☐	Fairly severe ☐	Very severe ☐
3. Walking How much have your symptoms interfered with your ability to walk in the last 2 weeks?	Not at all ☐	Slightly ☐	Moderately ☐	Severely ☐	Unable to walk ☐
4. Washing/Dressing How much have your symptoms interfered with your ability to wash or dress yourself in the last 2 weeks?	Not at all ☐	Slightly ☐	Moderately ☐	Severely ☐	Unable to wash or dress myself ☐
5. Physical activity levels How much has it been a problem for you to do physical activities (e.g. going for a walk or jogging) to the level you want because of your joint or muscle symptoms in the last 2 weeks?	Not at all ☐	Slightly ☐	Moderately ☐	Very much ☐	Unable to do physical activities ☐
6. Work/daily routine How much have your joint or muscle symptoms interfered with your work or daily routine in the last 2 weeks (including work & jobs around the house)?	Not at all ☐	Slightly ☐	Moderately ☐	Severely ☐	Extremely ☐
7. Social activities and hobbies How much have your joint or muscle symptoms interfered with your social activities and hobbies in the last 2 weeks?	Not at all ☐	Slightly ☐	Moderately ☐	Severely ☐	Extremely ☐

Arthritis Research UK MusculoSkeletal Health Questionnaire (MSK-HQ)

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NHS National Institute for Health Research

ParticipantID_____Date____Time_____StudyID 244266

Arthritis Research UK

NHS England

8. Needing help How often have you needed help from others (including family, friends or carers) because of your joint or muscle symptoms in the last 2 weeks?	Not at all ☐	Rarely ☐	Sometimes ☐	Fre-quently ☐	All the time ☐
9. Sleep How often have you had trouble with either falling asleep or staying asleep because of your joint or muscle symptoms in the last 2 weeks?	Not at all ☐	Rarely ☐	Sometimes ☐	Fre-quently ☐	Every night ☐
10. Fatigue or low energy How much fatigue or low energy have you felt in the last 2 weeks?	Not at all ☐	Slight ☐	Moderate ☐	Severe ☐	Extreme ☐
11. Emotional well-being How much have you felt anxious or low in your mood because of your joint or muscle symptoms in the last 2 weeks?	Not at all ☐	Slightly ☐	Moderately ☐	Severely ☐	Extremely ☐
12. Understanding of your condition and any current treatment Thinking about your joint or muscle symptoms, how well do you feel you understand your condition and any current treatment (including your diagnosis and medication)?	Comple-tely ☐	Very well ☐	Moderately ☐	Slightly ☐	Not at all ☐
13. Confidence in being able to manage your symptoms How confident have you felt in being able to manage your joint or muscle symptoms by yourself in the last 2 weeks (e.g. medication, changing lifestyle)?	Extre-mely ☐	Very ☐	Moderately ☐	Slightly ☐	Not at all ☐
14. Overall impact How much have your joint or muscle symptoms bothered you overall in the last 2 weeks?	Not at all ☐	Slightly ☐	Moderately ☐	Very much ☐	Extremely ☐

15. Physical activity levels

In the **past week**, on how many days have you done a total of 30 minutes or more of physical activity, which was enough to raise your heart rate? *This may include sport, exercise and brisk walking or cycling for recreation or to get to and from places, but should not include housework or physical activity that is part of your job.*

None	1 day	2 days	3 days	4 days	5 days	6 days	7 days
☐	☐	☐	☐	☐	☐	☐	☐

Finally, please check back that you have answered each question. Thank you very much.

Appendix 3

Missing data information

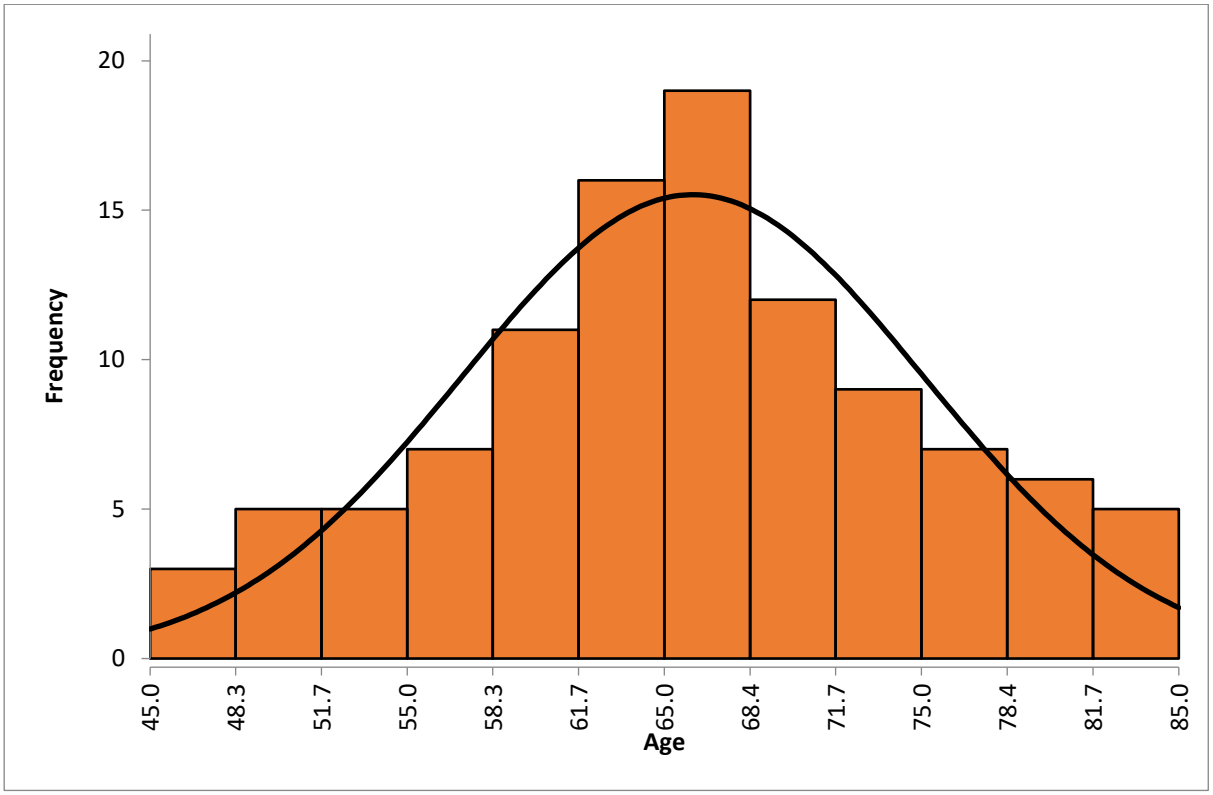
Variable	Sub-Variable	Data missing in control group (Baseline)	Data missing in control group (Follow up)	Data Missing in intervention group (Baseline)	Data Missing in intervention group (Follow up)
NRS Pain		0	0	0	0
WOMAC	Pain	0	0	0	0
	Stiffness	1	0	0	1
	Physical Function	2	1	0	0
TUG		0	0	0	0
30CST		0	0	0	0
MSK-HQ		1	1	2	1
PPT	Superolateral Patella	0	0	0	0
	Superomedial Patella	0	0	0	0
	Medial Joint line	0	0	0	0
	Tibialis Anterior Muscle	0	0	0	0
Temporal Summation (TS)		0	0	0	0

Conditional Pain Modulation (CPM)		0	0	0	0
Isokinetic Peak Torque	Q60	0	0	0	0
	H60	0	0	0	0
	Q180	0	0	0	0
	H180	0	0	0	0
Pittsburgh Sleeping Quality Index (PSQI)		0	2	1	0
Actigraphy Data	Time in Bed	0	0	0	0
	Total Sleep Time	0	0	0	0
	Onset Latency	0	0	0	0
	Wakefulness occurring after defined sleep onset (WASO)	0	0	0	0
	Sleep efficiency	0	0	0	0
Musculoskeletal Ultrasound	Synovial Fluid	0	0	0	0
	Synovial Hypertrophy	0	0	0	0
	Hypervascularity	0	0	0	0

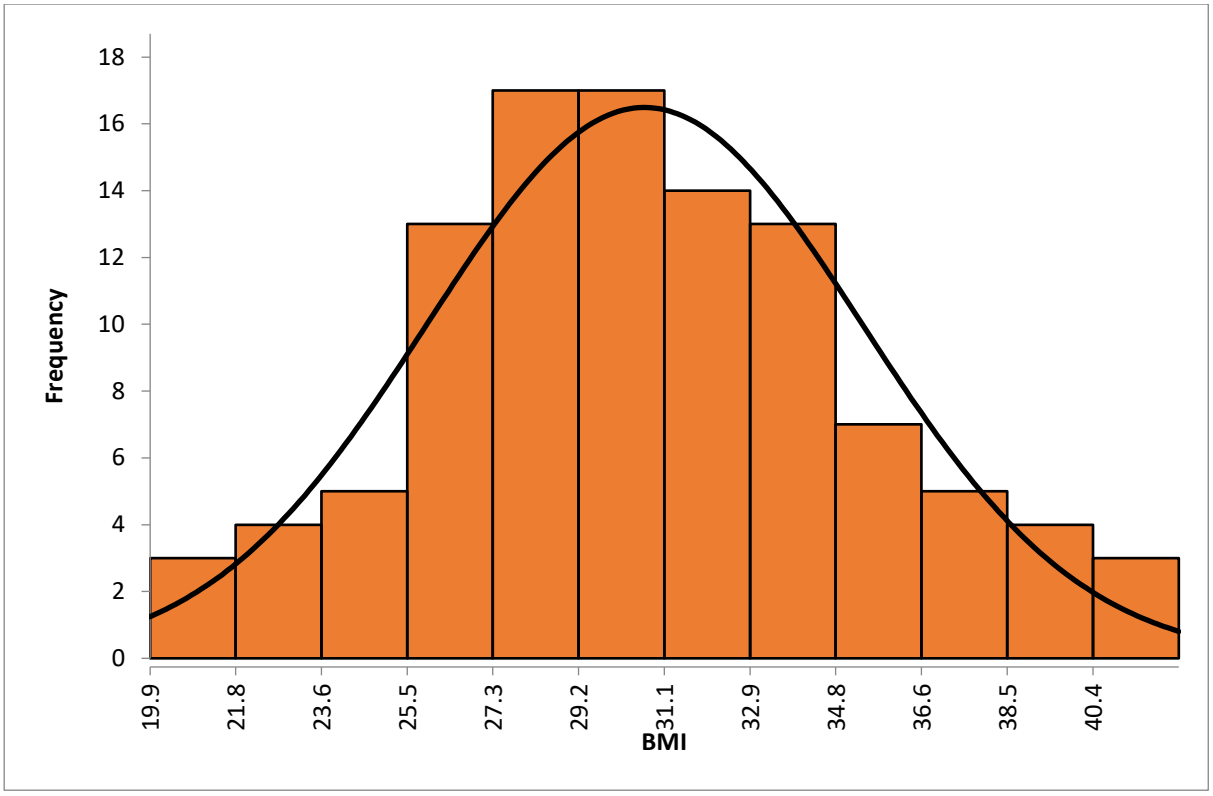
Appendix Table 1: Missing Data Itemized. **NRS Pain**, 0-10 where 0 is no pain and 10 is the worst pain imaginable. **WOMAC** items are scored on a scale of 0-4 (lower scores indicate lower levels of Pain (5 items, 0-20), stiffness (2 items, 0-8), and physical function (17 items, 0-68). **TUG** is measured in seconds, the participant stands up upon the therapist's command, walks 3 meters, turns around, walks back to the chair and sits down. **30CST** Counts the number of times the participant comes from a sitting position on a chair to a full standing position in 30 seconds. **PPT, TS, CPM** (0 to maximum value). **The isokinetic peak torque** (Newton meter) of quadriceps and hamstring muscles measured at 60 degrees/second and at 180 degrees/second. **MSK-HQ**, 14 questions scored on a scale of 0-4 (lower scores indicate lower levels of symptoms or physical disability), the total score is the sum of all items. **PSQI**, 7 components consisting of 9 questions providing an overall score ranging from 0 to 21, where higher scores denote a disturbed sleep quality. **Actigraphy Data**, a device to monitor sleeping pattern and has 5 subcomponents as shown above. **Musculoskeletal Ultrasound**, it has three subcomponents as mentioned above.

Appendix 4

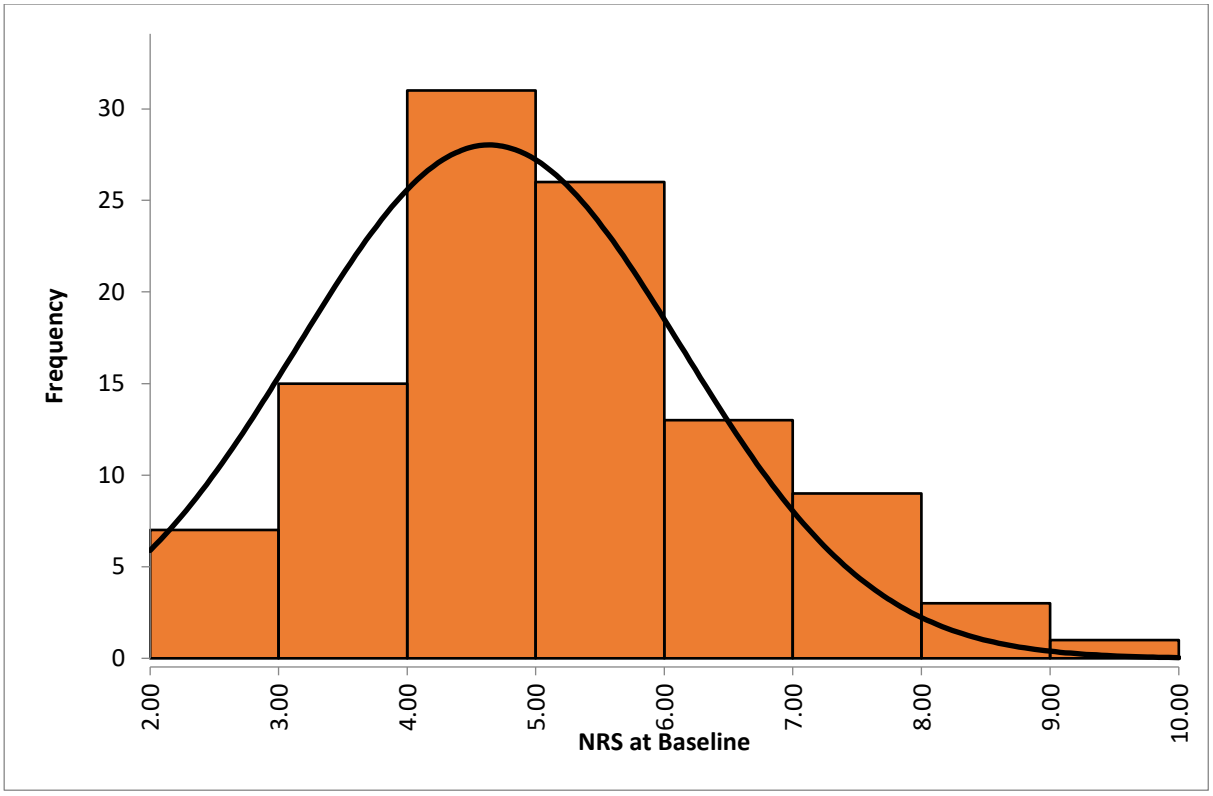
Histograms for demographics and outcome measures



Histogram for Age of both groups at baseline

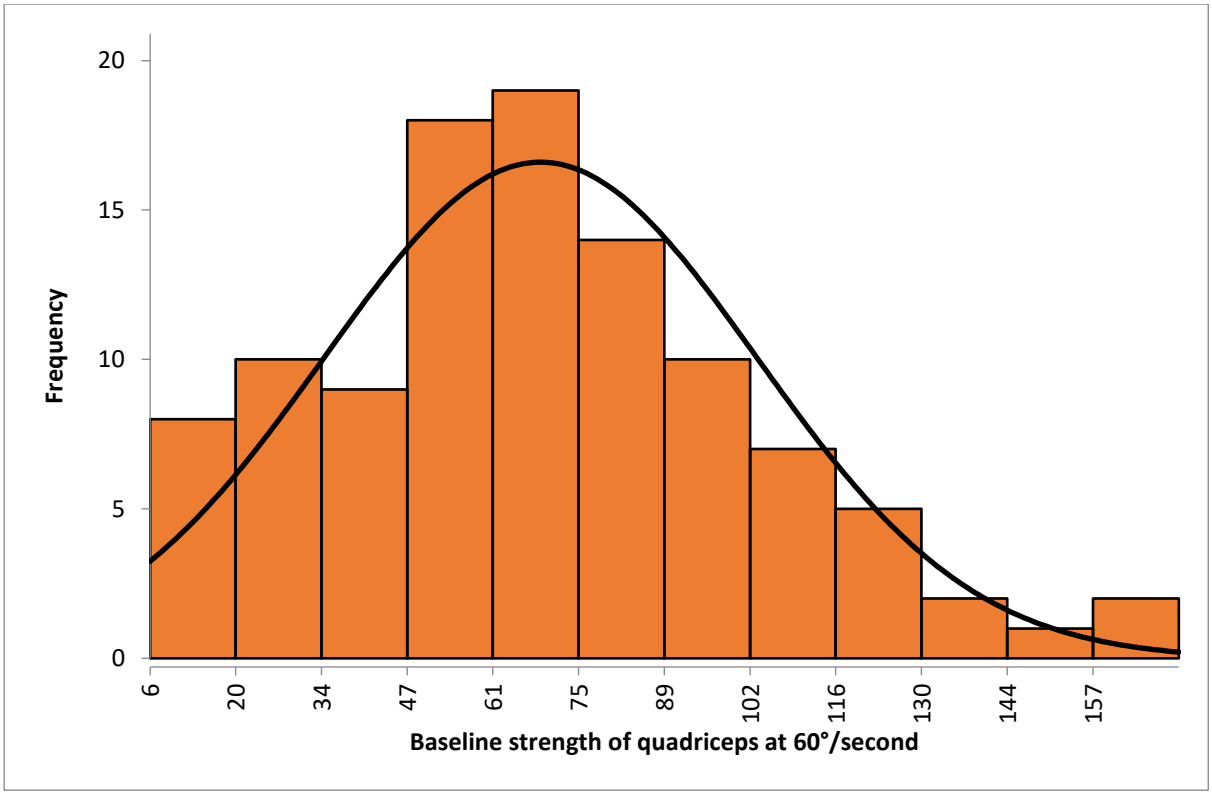


Histogram of BMI for both groups at baseline

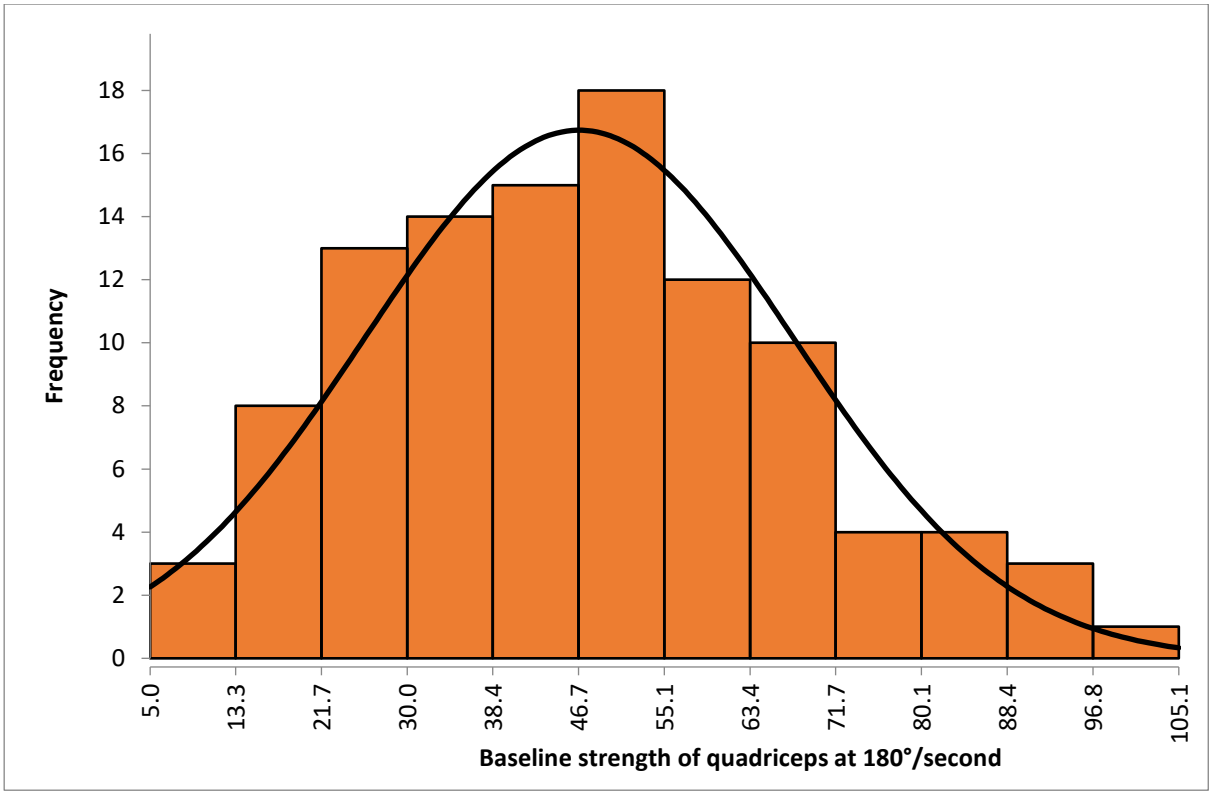


Pain score on Numerical Rating Scale (NRS) for both groups at baseline

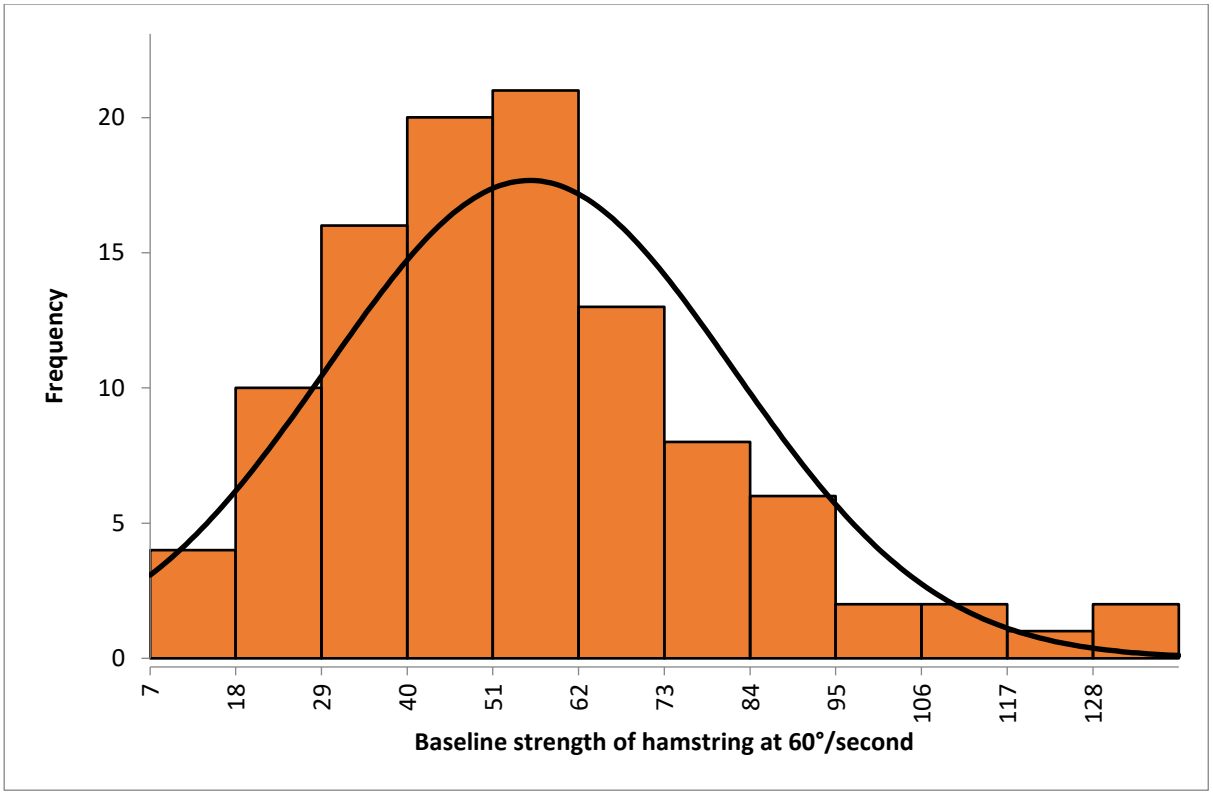
(Range 0-10, with 0 indicating no pain and 10, the worst pain imaginable)



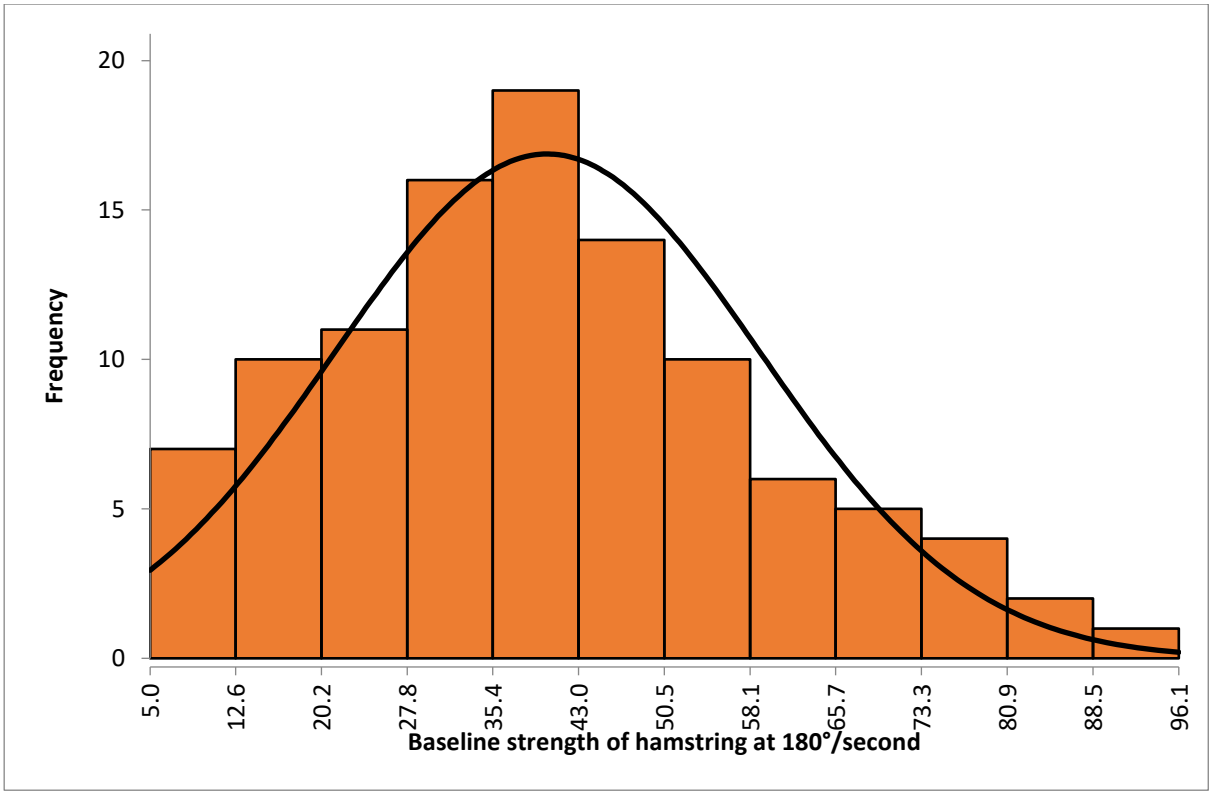
Isokinetic Strength Testing of quadriceps at 60°/second for both groups at baseline (Newton meter)



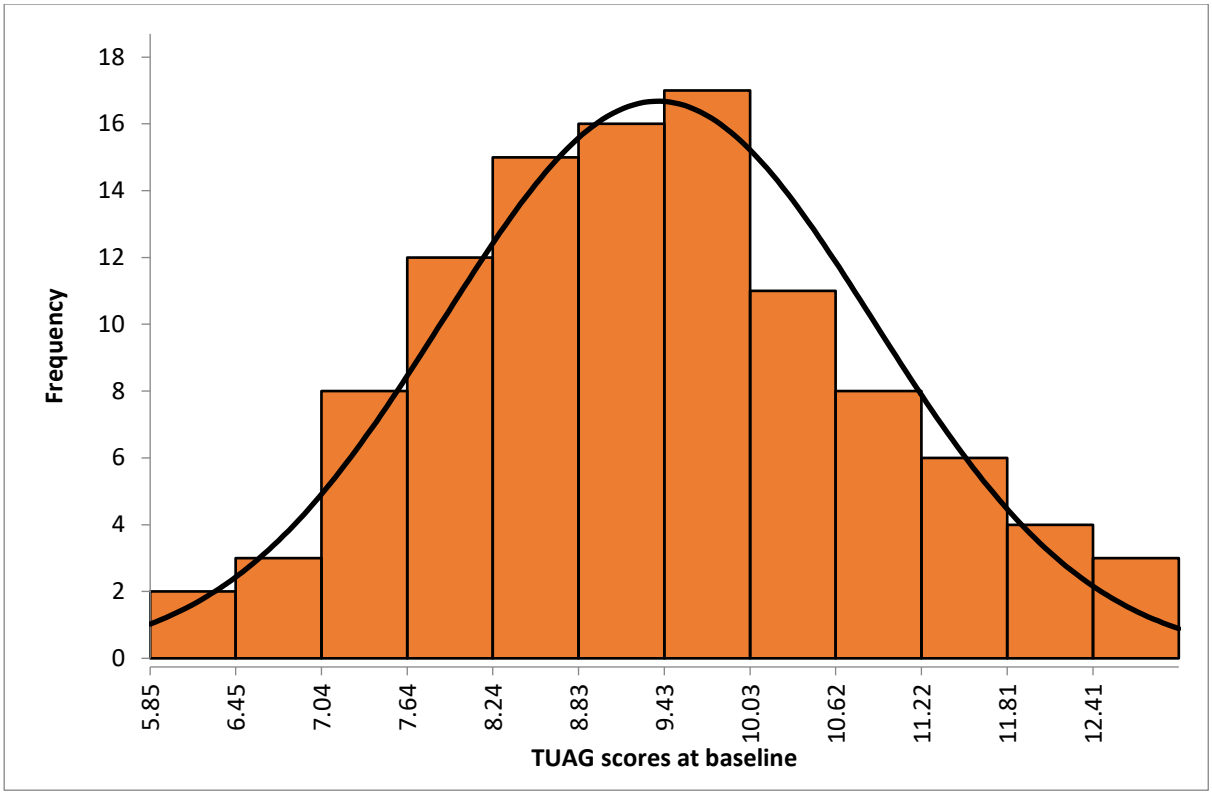
Isokinetic Strength Testing of quadriceps at 180°/second for both groups at baseline (Newton meter)



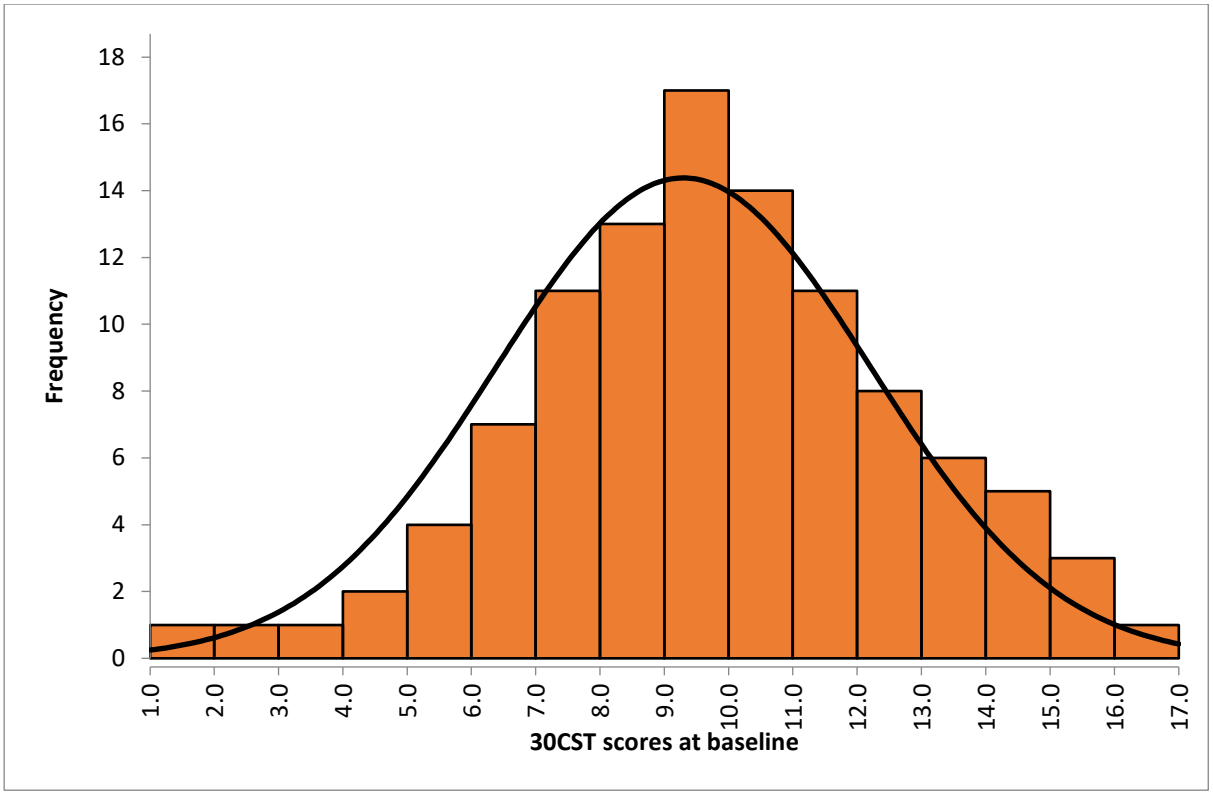
Isokinetic Strength Testing of hamstring at 60°/second for both groups at baseline (Newton meter)



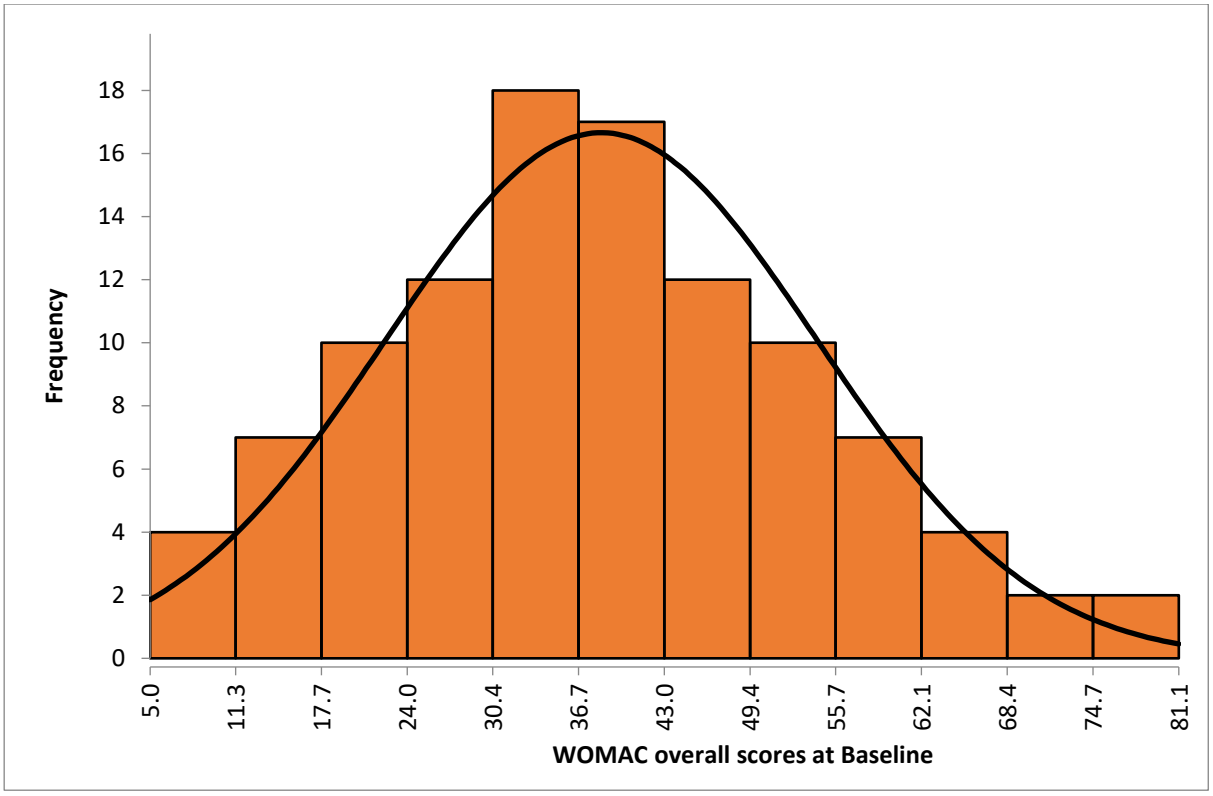
Isokinetic Strength Testing of hamstring at 180°/second for both groups at baseline (Newton meter)



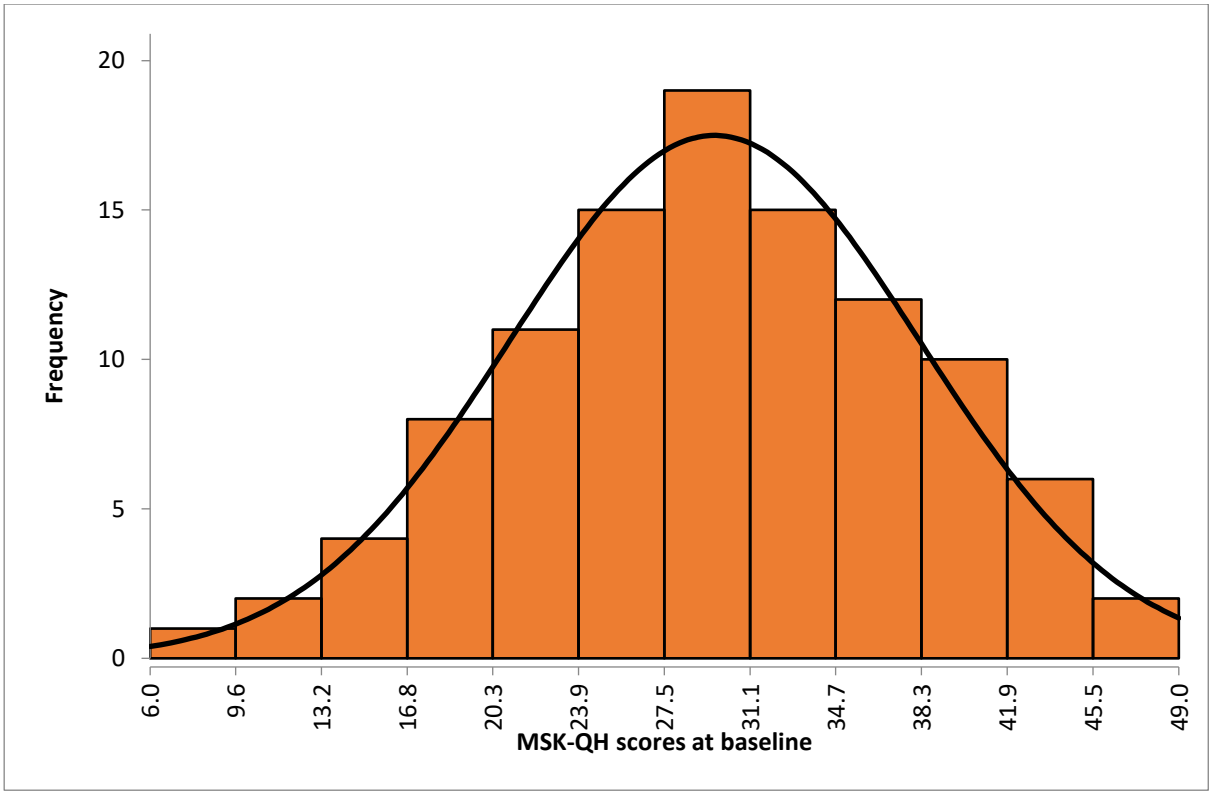
Timed up and Go (TUAG) scores for both groups at baseline (measured in seconds)



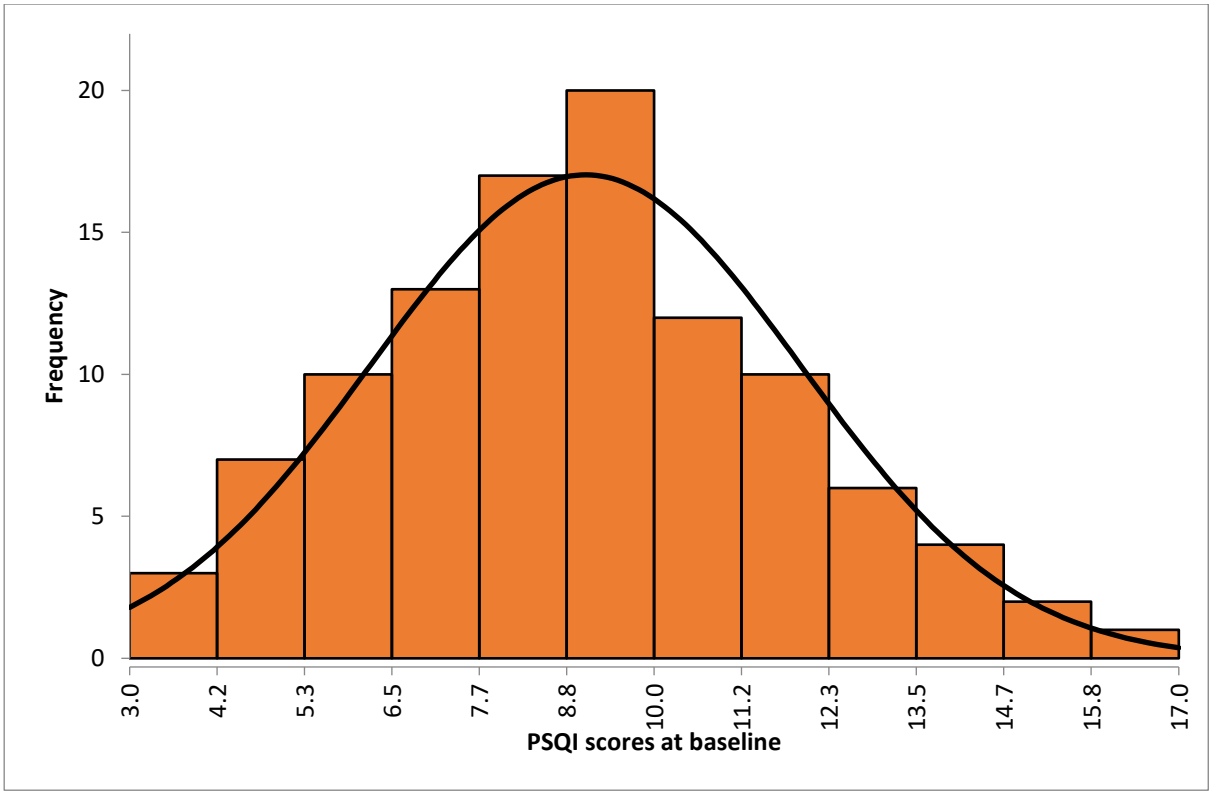
30 Second sit to stand test (30CST) score for both groups at baseline (counts)



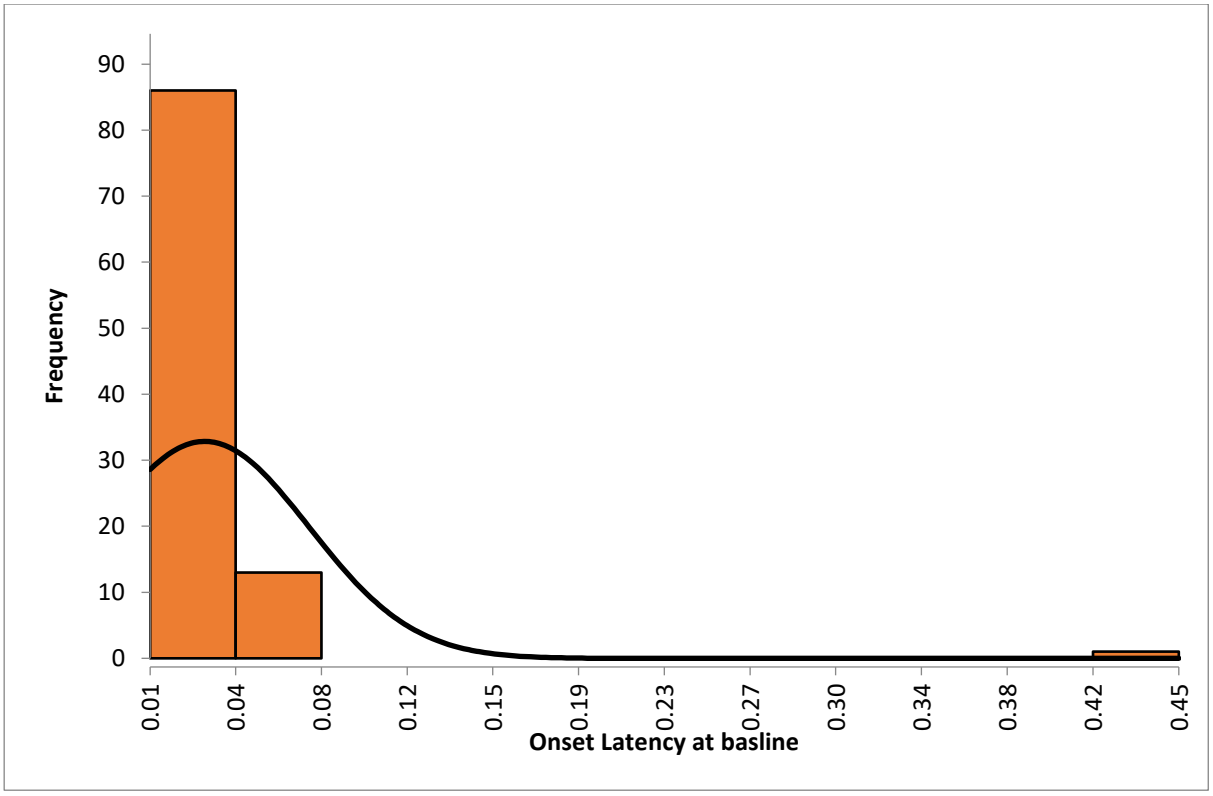
The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) overall scores for both groups at baseline (Range from 0-96 for overall scores)



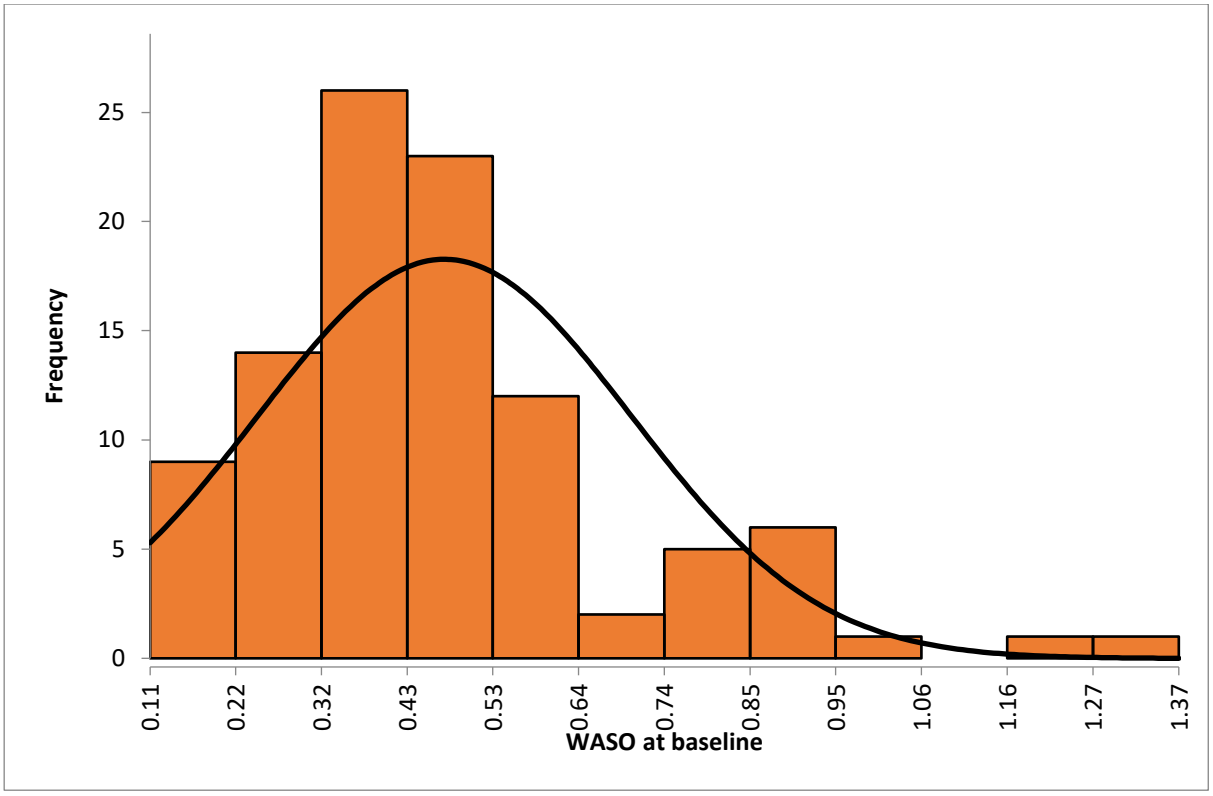
The Musculoskeletal Health Questionnaire (MSK-HQ) Scores for both groups at baseline (range from 0-56)



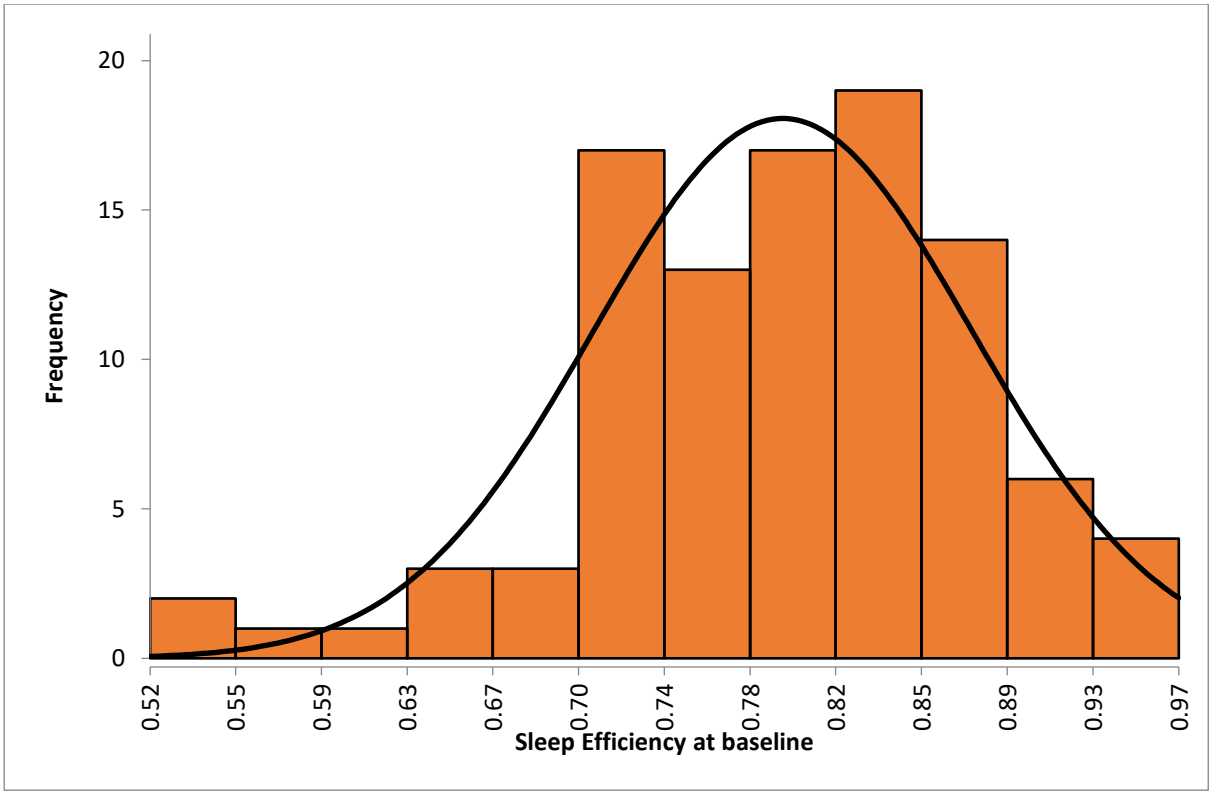
Pittsburgh Sleep Quality Index (PSQI) score for both groups at baseline (ranges from 0-21)



Onset Latency for both groups at baseline (Hours)



Wake after sleep onset (WASO) for both groups at baseline (Hours)



Sleep efficiency for both groups at baseline (Percentage divided by 100)