National Institute for Health and Care Excellence

Draft for consultation

Osteoarthritis: assessment and management (update)

[E] Evidence reviews for the clinical and cost-effectiveness of manual therapy for the management of osteoarthritis

NICE guideline <number>

Evidence reviews underpinning recommendations 1.3.6 to 1.3.7 and research recommendations in the NICE guideline

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1 Manual therapy

1.1 Review question

What is the clinical and cost-effectiveness of manual therapy for the management of osteoarthritis?

1.1.1 Introduction

The benefit of exercise for people with some forms of osteoarthritis is well established. Manual therapy may also help provide a benefit for some joints by increasing mobility and reducing pain. There are a variety of techniques including passive stretching, soft tissue techniques and acupressure/trigger point therapy.

There is no standard current practice relating to the provision of manual therapy for people with osteoarthritis, the use of this management approach is left to the discretion and expertise of the treating healthcare professional. As manual therapy needs to be delivered in a face-to-face context, there is potentially a resource implication for offering manual therapy in a system in which remote consultations are employed. This review aims to investigate the effectiveness of manual therapy (including passive and active mobilisation) and manual therapy plus exercise compared to exercise or no manual therapy in the management of osteoarthritis to establish whether manual therapy should be offered to people with osteoarthritis.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Exclusion: • Children (age ≤16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy).
Interventions	Interventions (minimum duration 1 week): • Manual therapy alone • Manual therapy and exercise combined Manual therapy will be pooled in the analysis and interventions may include: • Manipulation and/or mobilisation (joint or neurodynamic mobilisation, traction) • Passive stretching • Soft tissue techniques • Acupressure/ trigger point therapy • Combined active and passive manual therapy
Comparisons	• Exercise (Compared to manual therapy and exercise only) • Sham manual therapy • No manual therapy intervention (including either):

	○ Manual therapy versus no treatment* ○ Manual therapy plus additional treatment versus additional treatment alone** *No treatment defined as either (1) doing nothing or (2) very low intensity intervention such as advice **Inclusion of studies where additional treatment is the same in each arm will be assessed on a case by case basis. Studies including high intensity additional treatment may not be included due to the risk that treatment could have an interaction with the intervention of interest and mask the true treatment effect.
Outcomes	Stratify by ≤/>3 months (longest time-point in each): Primary outcomes: • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] Secondary outcomes: • Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [validated patient-reported outcomes, continuous data prioritised] • Minor adverse events [dichotomous] • Moderate/major adverse events [dichotomous]
Study design	• Systematic reviews of RCTs • Parallel RCTs

A range of non-pharmacological interventions have been reported to reduce joint pain and improve function. However, these interventions are not used consistently. This review aims to assess the clinical and cost-effectiveness of manual therapy (including passive and active mobilisation) in the management of osteoarthritis. A minimum duration of one week was thought relevant to ensure that the participants received more than one session of the intervention.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Fifteen randomised controlled studies were included in the review;[1, 2, 5, 12, 32, 33, 48, 51, 55, 77, 82, 86, 87, 95, 105] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

The clinical studies identified included the following comparisons:

- Manual therapy compared to sham therapy
- Manual therapy compared to no treatment
- Manual therapy and exercise compared to exercise
- Manual therapy and exercise compared to sham therapy
- Manual therapy and exercise compared to no treatment

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

Most of the studies were in combination with exercise and the majority of studies included participants with osteoarthritis of the knee.

1.1.4.2 Excluded studies

There were relevant systematic reviews, which did not meet the PICO for inclusion completely with the main difference being the comparators. The references were checked any studies that fulfilled the inclusion criteria were included.

See the excluded studies list in Appendix I.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Abbott 2013[2] Subsidiary paper: Abbott 2019[3]	**Manual therapy** (n=54) Procedures to modify quality and range of motion of the target joint and associated soft tissue structures. 9 treatment sessions of 50 minutes. Additional individual interventions prescribed and home programme of joint range of motion activities x3 per week. Usual care offered by GP or their healthcare providers. **No treatment** (n= 51) Usual care offered by GP or their healthcare providers. **Manual therapy and exercise** (n=50) Same manual therapy approach explained previously, with an exercise program consisting of a multi-modal supervised programme of warm-up/aerobic, muscle strengthening, muscle stretching and neuromuscular control exercises. Additional exercises were prescribed individually for each participant on the basis of the physical examination findings. In	**Hip or knee osteoarthritis** Mean age (SD): 67.3 (10.2) years manual therapy + usual care; 66.1 (10.7) years usual care control N = 206 Definition: American College of Rheumatology criteria for hip or knee osteoarthritis Severity: pain intensity score 4.2 (2.3) versus 3.1 (2.0); Duration of symptoms: duration since first diagnosis of OA 2.5 (1.4) versus 2.8 (1.3). Presence of multi-morbidities: Not stated/unclear	Pain at >3 months Moderate/major adverse events at >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	addition participants completed the home exercise programme prescribed to all participants **Exercise** (n=51) Exercise programme only **Concomitant therapy:** Not stated			
Abbott 2015[1] Subsidiary paper: Pryymachenko 2021[85]	**Manual therapy and exercise** (n=18) 12 sessions of 30-45 minutes: knee flexion, anteroposterior-directed force, knee extension, posteroanterior-directed force, patellar gliding force, manual stretch, soft tissue manipulation. Secondary (nonmandatory) interventions prescribed when indicated by assessment findings. Home program of reinforcing activities plus 12 sessions for 45 minutes of multimodal exercise therapy supervised by a physical therapist. **Exercise** (n=19) 12 sessions for 45 minutes of multimodal exercise therapy supervised by a physical therapist **Concomitant therapy:** Not reported	**Knee osteoarthritis** Mean age (SD): 61 (12) years for manual therapy + exercise versus exercise 64 (10) years N=75 Definition: American College of Rheumatology clinical criteria for a diagnosis of knee osteoarthritis Severity: pain intensity score (VAS 0-10) 2.8 (1.9); 2.1 (1.2) Duration of symptoms: ≤ 1 year: 4 versus 3; 1-2 years: 4 versus 2; 3-5 years: 1 versus 3; 5-10 years: 2 versus 9; > 10 years: 7 versus 2. Presence of multi-morbidities: not stated.	Pain at >3 months Moderate/major adverse events at >3 months	
Akbarnezhad 2019[5]	**Manual therapy** (n=15)	**Knee osteoarthritis**	Pain at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Acupressure/trigger point therapy. 10 continuous 15 minute sessions for 3-4 weeks. **Sham manual therapy** (n=15) Targeting non-acupoints. Same number of sessions. **No treatment** (n=21) **Concomitant therapy:** Not reported	Age range: 60-95 years N = 51 Definition: Diagnosed by a rheumatologist and based on x-ray. Severity: Not stated/unclear Duration of symptoms: Between 1-15 years. Presence of comorbidities: Not stated/unclear	Physical function at ≤3 months	
Altinbilek 2018[12]	**Manual therapy and exercise** (n=50) 3 minutes mobilisation, 3 minutes compression for bilateral patellofemoral and tibiofemoral joint respectively with one minute intervals plus exercise 10 repetitive 3 sets, 2 days per week, total of four sessions. **Exercise** (n=50) 10 repetitive 3 sets, 2 days per week, total of four sessions. **Concomitant therapy:** Patients were not allowed to take NSAIDs one week before beginning of study and during the study period. They were allowed to take paracetamol up to 3g daily for pain control. Drugs they used for systemic diseases continued.	**Knee osteoarthritis** Mean age (SD): 54.8 (8.5) years N = 100 Definition: Diagnosed as bilateral primary knee OA according to the American College of Rheumatology criteria. The anteroposterior and lateral knee radiographs taken to stage OA according to the Kellgren and Lawrence radiological staging scale. Severity: Kellgren 2: 33 (75%) versus 33 (80.5%); Kellgren 3: 11 (25%) versus 8 (19.5%). Duration of symptoms: median 2 (0.25 to 15) versus 2 (0.25 to 15).	Pain at ≤3 months Physical function at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		Presence of multi-morbidities: 25 (56.8%) versus 29 (70.7%)		
Cheung 2020[32]	**Manual therapy** (n= 17) Participants in the acupressure group received two weekly 90 minute self-administered acupressure training sessions (groups of 4-6) delivered by a registered Chinese Medicine practitioner with at least 5 years of clinical experience in acupuncture and acupressure. **No treatment** (n= 18) Participants in this group attended two weekly 90 minute health education sessions related to KOA management delivered by a registered nurse. Concomitant therapy: Participants in both groups received follow-up phone calls twice per week for 6 weeks. Participants were advised to maintain their routine medical care for KOA, including medications and physician visits.	**Knee osteoarthritis** Mean age (SD): 62.14 (5.93) years N = 35 Definition: A diagnosis of knee OA based on fulfilment of any 3 of the clinical criteria developed by Altman et al (morning stiffness≤ 30 min, crepitus on active joint motion, bone tenderness, bone enlargement and no palpable joint warmth). Severity (pain intensity score): 9.06 (0.71) versus 9.00 (0.69) Duration of symptoms (months: 51.35 (46.91) versus 51.53 (79.21) Presence of multi-morbidities: Not stated/unclear	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Minor adverse events at ≤3 months	
Choi, 2019[33]	**Manual therapy** (n= 15) The experimental group received a knee joint traction workout for 20 minutes a day, five times a week.	**Knee osteoarthritis** Mean age (SD): manual therapy group: 67.53 (4.13) years; no treatment group: 65.40 (4.88) years N = 30	Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	No treatment (n= 15) **Concomitant therapy:** Both groups received general physical therapy, which was carried out in three ways and included 20 minutes of superficial heat therapy, 5 minutes of deep heat therapy and 20 minutes of electric therapy five times a week.	Definition: Patients had been diagnosed by their attending doctors with knee degenerative arthritis based on clinical findings and X-ray images. Severity: (K-L grade, %): 2.26 (0.45) versus 2.66(0.61) Duration of symptoms: (not stated whether this is months): Knee joint traction group: 12.06 (2.01) versus 13.06 (2.21) Presence of multi-morbidities: Not stated/unclear		
Fitzgerald 2016[48]	**Manual therapy and exercise** (n=75) 9 weeks. Manoeuvres applied with manual force from the treating therapist, with techniques based on those recommended for reducing pain and improving function in people with knee OA. Core MT techniques included those specifically addressing knee joint mobility/flexibility and soft tissue manipulations. Additional but optional manual techniques were provided if indicated by deficits on initial examination. Plus exercise: 9 weeks, 45	**Knee osteoarthritis** Mean age (SD): 58 (9.8) manual therapy plus exercise group; 53.3 (10) exercise group years N = 300 Definition: American College of Rheumatology clinical criteria for knee osteoarthritis Severity: knee pain rating scale 5.4 (2.4) versus 5.7 (2.3). Duration of symptoms:	Pain at ≤3 months and >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	minutes to an hour: an aerobic warm-up then series of strengthening, stretching and neuromuscular control (agility and balance training techniques), considered core exercises. The therapists had the option to select additional exercise activities, based on initial examination findings. **Exercise** (n=75) 9 weeks, 45 minutes to an hour: an aerobic warm-up then series of strengthening, stretching and neuromuscular control (agility and balance training techniques), considered core exercises. The therapists had the option to select additional exercise activities, based on initial examination findings. **Concomitant therapy:** All participants received 12 supervised therapy sessions	≤ 1 year 8 (10.7%); 9 (12%) 1-2 years 12 (16%); 7 (9.3%) 3-5 years 14 (18.7%); 13 (17.3%) 5-10 years 25 (33.3%); 27 (36%) > 10 years 16 (21.3%); 19 (25.3%). Presence of multi-morbidities: 1: 19 versus 24; 2: 26 versus 20; >2: 17 versus 19.		
French 2013[51] Subsidiary paper: French 2009[52]	**Manual therapy and exercise** (n=43) Up to 15 minutes of manual therapy in line with current clinical practice at participating sites. A choice of non-manipulative manual therapy techniques based on pain/stiffness relations and movement restrictions of the	**Hip osteoarthritis** Mean age (SD): 61.43 (10.76) in the manual therapy plus exercise group, 62.44 (0.09) in the exercise group. N = 131 Definition:	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months	This study reports long term outcomes, but these could not be included as the no treatment arm group was re-randomised to the other treatment arms at 9 weeks.

Study	Intervention and comparison	Population	Outcomes	Comments
	affected hip was available, with no more than 5 manual therapy techniques allowed during an individual session. Plus 30 minutes of flexibility and strengthening exercises delivered using a semi-structured protocol **Exercise** (n=45) 30 minutes of flexibility and strengthening exercises delivered using a semi-structured protocol. **No treatment** (n=43) Waiting list control for 9 weeks (after this time participants were re-randomised to the other treatment arms) **Concomitant therapy:** All groups received standardised written information on hip OA. All other interventions were avoided for the duration of the RCT, apart from routine doctor care and analgesics. Participants with bilateral hip OA received clinic-based treatment for the more symptomatic hip only, but were provided with an HEP for both hips	Osteoarthritis of the hip according to the American College of Rheumatology and radiographic criteria Severity: pain with activity: 5.88 (2.28) versus 5.64 (2.80) Duration of symptoms: 36.43 (51.75) Presence of multi-morbidities: 2.38 (1.45) versus 1.97 (1.36).		
Guo 2021[55]	**Manual therapy and exercise** (n=55) Acupressure (self managed) and mixed aerobic and	**Knee osteoarthritis** Mean age (SD): 62.7 (7.9) years N = 221	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	strengthening exercise program taught over eight weeks and completed over sixteen weeks. To be conducted three times a week at home. **Manual therapy** (n=55) Acupressure regimen only. **Exercise** (n=56) Exercise only **No treatment** (n=55) **Concomitant therapy:** No additional information	Definition: Knee osteoarthritis by the American College of Rheumatology clinical criteria Severity: Not stated/unclear Duration of symptoms (mean [SD]): 5.9 (5.4) years Presence of multi-morbidities: Not stated/unclear		
Nigam 2021[77]	**Manual therapy and exercise** (n= 20) Mobilisation with movement plus exercise and moist heat. All participants attended the clinic for six 45 minute treatment sessions carried out over two consecutive weeks. **Exercise** (n=20) An exercise programme designed to improve muscle strength of the hip, knee and ankle musculature. Exercises included pelvic bridging, resisted knee flexion and extension, mini squats and heel raises. All participants attended the clinic for six 45 minute	**Knee osteoarthritis** Mean age (SD): manual therapy group: 58.5 (4.36) years, control group: 59.4 (6.57) years N=40 Definition: Diagnosis made by an orthopaedic surgeon based on American College of Rheumatology clinical criteria Severity: 6.4 (1.4) versus 6.3 (1.3) Duration of symptoms (months [SD]): 9.6 (9.73) versus 9.8 (9.34)	Pain at ≤3 months and >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment sessions carried out over two consecutive weeks. **Concomitant therapy:** All participants received moist heat for 15 minutes from a hydrocollator pack wrapped in soft towel applied around the affected knee.	Presence of multi-morbidities: Not stated/unclear		
Pollard 2008[82]	**Manual therapy** (n=26) A non-invasive Myofasical Mobilisation procedure and an impulse thrust procedure performed on the symptomatic knee. In cases where OA was bilateral; mobilisation was performed on both knees. Duration 3 treatments per week for 2 consecutive weeks. **Sham manual therapy** (n=17) A palmar contact to the knee without the application of force followed by interferential set at zero. The participants were told that the procedure was a micro current application that they should not be able to feel. . Duration 3 treatments per week for 2 consecutive weeks **Concomitant therapy:** Not stated	**Knee osteoarthritis** Mean age: 56.5 years N = 43 Definition: A prior medical diagnosis of OA in the knee(s) as per Forma et al (1983) and identification of the appearance of OA in one or both knees on radiographs. Severity: 3.3 (2.6 to 4.0) versus 3.5 (2.2 to 4.7). Duration of symptoms: Chronic, non-progressive history of osteoarthritic knee pain of at least one year. Presence of multi-morbidities: not stated.	Pain at ≤3 months	
Rani, 2020[87]	**Manual therapy** (n= 106) A protocol for acupressure technique was designed by the	**Knee osteoarthritis** Mean age (SD): 58.07 (11.2) years	Pain at ≤3 months and >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	investigators on the basis of literature review. The total duration of each session of acupressure therapy was limited to 15 minutes, consisting of 3 minutes of initial message around acupoints and 12 minutes of pressure applied on acupoints (2 minutes for each acupoint). Frequency of acupressure application was two times a day for five days in a week, for which a record was kept by patients in the logbook. **No treatment** (n= 106) **Concomitant therapy:** Pharmacological treatment (NSAIDs) was available to all participants	N = 212 Definition: Grade 2-3 Kellgren Lawrence scale knee osteoarthritis Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: not reported Presence of multi-morbidities: Charlson co-morbidity score: overall sample: 0 (17.34%), 1 (49.60%), >=2 (33.06%)	Psychological distress at ≤3 months and >3 months	
Rani 2021[86]	**Manual therapy** (n=80) Acupressure therapy self administered five times for 3 minutes twice daily for 12 months and pharmacological treatment. **Sham manual therapy** (n=80) Same therapy device but applied to non-acupoints and pharmacological treatment. **No treatment** (n=80) Pharmacological treatment only (type of therapy not specified).	**Knee osteoarthritis** Mean age (SD): 59.34 (6.57) years N = 240 Definition: Knee osteoarthritis by the American College of Rheumatology clinical criteria and radiological score Severity: Kellgren Lawrence grade 0-4, median grade 2 Duration of symptoms (SD): 5.10 (1.34) years	Quality of life at ≤3 months and >3 months Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: No additional information	Presence of multi-morbidities: Not stated/unclear		
Sit 2018[95]	**Manual therapy and exercise** (n=104) 5 minutes patellar mobilisation therapy followed by 5 minutes supervised non-load vastus medialis oblique exercise. Trained primary care physicians performed all interventions. **No treatment** (n=104) waiting list control group. Participants were contacted by telephone at the same interval as the manual therapy group sessions, and completed outcome measures in the same time frame. **Concomitant therapy:** Both had standard care of conventional medication, physical therapy, acupuncture, herbal and over-the counter drugs, and other active treatments were allowed. They did not restrict either physicians or patients from providing or seeking other interventions during the study period.	**Knee osteoarthritis** Mean age (SD): 60.2 (5.7) years N = 208 Definition: A diagnosis of knee osteoarthritis based on clinical and radiographic criteria defined by the American Rheumatology Association. Severity: Knee pain intensity, mean (SD): intervention group 62.6 (17.5); control group 63.6 (17.4). Duration of symptoms: Duration of knee pain, mean (SD): intervention group 6.9 (5.5) years; control group 8.5 (7.4) years. Presence of multi-morbidities: 1: 35 (33.7%) versus 33 (31.7%); 2: 32 (30.8) versus 32 (30.8); >/=3: 37 (35.6) versus 39 (37.5%).	Quality of life at >3 months Pain at >3 months Physical function at >3 months	
Villafane 2013[105]	**Manual therapy and exercise** (n=30) 12 sessions over 4 weeks (3 sessions per week). Joint	**Hand osteoarthritis** Mean age (SD): 82 (6) years N = 60	Pain at ≤3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	mobilisation applied for 3 minutes with 1 minute rest period, repeated 3 times. Neurodynamic slider technique performed twice for 5 minutes each time, with a 1-minute rest between sets. Exercise: standardised exercise protocol as that described by Rogers and Wilder. The first 6 exercises consisted of active range-of-motion movements of the hand that were designed to improve joint flexibility. The remaining 3 exercises were designed to strengthen grip and pinch strength by using a non-latex polymer ball hand exerciser. **Sham manual therapy** (n=30) Received the same number of treatment sessions as those in the manual therapy group but received in-active doses of pulsed ultrasound with an with an intensity of 0 W/cm2 and gentle application of an inert gel for 10 minutes to the hypothenar areas of the symptomatic hand. Duration Similar to manual therapy group. **Concomitant therapy:** Not stated	Definition: Diagnosis established by a hand surgeon. Each patient underwent subjective and physical examination, performed by a physical physiotherapist experienced in musculoskeletal physiotherapy and was evaluated for inclusion/exclusion in the study. A diagnosis of stage III or IV secondary CMC joint OA in the dominant hand, according to the Eaton-Littler-Burton classification system based on radiographic findings was required. Severity: pain: 5.0 (0.3) versus 5.0 (0.2). Duration of symptoms: not stated Presence of multi-morbidities: not stated		

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 5: Clinical evidence summary: manual therapy versus sham therapy

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with sham therapy	Risk difference with manual therapy	
Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 3 months	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 30.45	MD **2.31 lower** (6.3 lower to 1.68 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component, 0-100, high is good, final value) at ≤3 months	151 (1 RCT) follow up: 3 months	⊕⊕◯◯ LOW [a]	-	The mean quality of life was 51.24	MD **0.1 higher** (3.32 lower to 3.52 higher)	MID = 3 (established value)
Quality of life (SF-36 physical component, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 32.21	MD **1.66 higher** (1.82 lower to 5.14 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component, 0-100, high is good, final value) at >3 months	151 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [a]	-	The mean quality of life was 52.45	MD **3.53 higher** (0.33 lower to 7.39 higher)	MID = 3 (established value)
Pain (WOMAC, NRS [different scale ranges], high is poor, final values) at ≤3 months	222 (3 RCTs) follow up: mean 6 weeks	⊕◯◯◯ VERY LOW [a,b]	-	-	SMD **0.76 SD lower** (1.64 lower to 0.12 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, 0-20, high is poor, final value) at >3 months	151 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [a]	-	The mean pain was 11.04	MD **2.5 lower** (3.77 lower to 1.23 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, final value) at ≤3 months	179 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	-	-	SMD **0.53 SD lower** (1.45 lower to 0.39 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with sham therapy	Risk difference with manual therapy	
	follow up: mean 8 weeks					
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months	151 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [a]	-	The mean pain was 34.67	MD **3.47 lower** (7.1 lower to 0.16 higher)	MID = 0.5 SD (SMD)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

Table 3: Clinical evidence summary: manual therapy versus no treatment

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with manual therapy	
Quality of life (SF-6D, 6-31, high is poor, final value) at ≤3 months	35 (1 RCT) follow up: 6 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean quality of life was 0.744	MD **0.07 lower** (0.15 lower to 0.01 higher)	MID = 0.5 SD (SMD)
Quality of life (SF-36 physical component summary, 0-100, high is good, final value) at ≤3 months	160 (1 RCT) follow up: 3 months	⊕⊕◯◯ LOW [b]	-	The mean quality of life was 27.34	MD **0.79 higher** (2.09 lower to 3.67 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component summary, 0-100, high is good, final value) at ≤3 months	160 (1 RCT) follow up: 3 months	⊕⊕⊕◯ MODERATE [b]	-	The mean quality of life was 51.67	MD **0.33 lower** (3.16 lower to 2.5 higher)	MID = 3 (established value)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with manual therapy	
Quality of life (SF-36 physical component summary, 0-100, high is good, final value) at >3 months	150 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [b]	-	The mean quality of life was 30.85	MD **3.02 higher** (0.39 lower to 6.43 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component summary, 0-100, high is good, final value) at >3 months	150 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [b]	-	The mean quality of life was 51.78	MD **4.2 higher** (0.03 lower to 8.43 higher)	MID = 3 (established value)
Pain (WOMAC [different scale ranges], high is poor, final values) at ≤3 months	324 (4 RCTs) follow up: mean 8 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.66 SD lower** (1.38 lower to 0.06 higher)	MID = 0.5 SD (SMD)
Pain (NRS, 0-10, high is poor, change score and final value) at ≤3 months	242 (2 RCTs) follow up: mean 6 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean pain was 4.45	MD **2.34 lower** (4.35 lower to 0.53 higher)	MID = 1.40 (0.5 x median baseline SD)
Pain (NRS, 0-10, high is poor, change scores) at >3 months	306 (2 RCTs) follow up: mean 16 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean pain was 4.16	MD **1.91lower** (4.35 lower to 0.53 higher)	MID = 1.74 (0.5 x median baseline SD)
Physical function (WOMAC, 0-68, high is poor, change score) at ≤3 months	30 (1 RCT) follow up: 4 weeks	⊕⊕◯◯ LOW [a]	-	The mean physical function was -8.86	MD **13 lower** (15.53 lower to 10.47 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, final values) at ≤3 months	331 (4 RCTs) follow up: mean 8 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.51 SD lower** (0.95 lower to 0.06 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months	251 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	-	The mean physical function was 31.4	MD **5.23 lower** (8.27 lower to 2.18 lower)	MID = 3.9 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with manual therapy	
	follow up: 12 months					
Psychological distress (BDI, 0-63, high is poor, change score) at ≤3 months	30 (1 RCT) follow up: 4 - weeks	⊕⊕◯◯ LOW [a]	-	The mean psychological distress was -1.4	MD **7.13 lower** (9.38 lower to 5.89 lower)	MID = 0.5 SD (SMD)
Psychological distress (DASS-21 depression, 0-21, high is poor, final value) at ≤3 months	212 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b]	-	The mean psychological distress was 16.42	MD **2.14 lower** (4.51 lower to 0.23 higher)	MID = 0.5 SD (SMD)
Psychological distress (DASS-21 anxiety, 0-21, high is poor, final value) at ≤3 months	212 (1 RCT) follow up: 2 months	⊕⊕◯◯ LOW [a]	-	The mean psychological distress was 8.12	MD **1.22 higher** (0.22 lower to 2.66 higher)	MID = 0.5 SD (SMD)
Psychological distress (DASS-21 stress, 0-21, high is poor, final value) at ≤3 months	212 (1 RCT) follow up: 2 months	⊕⊕◯◯ LOW [a]	-	The mean psychological distress was 17.16	MD **1.93 lower** (4.31 lower to 0.45 higher)	MID = 0.5 SD (SMD)
Psychological distress (DASS-21 depression, 0-21, high is poor, final value) at >3 months	212 (1 RCT) follow up: 2 months	⊕⊕◯◯ LOW [a]	-	The mean psychological distress was 14.564	MD **3.58 lower** (8.11 lower to 0.94 higher)	MID = 0.5 SD (SMD)
Psychological distress (DASS-21 anxiety, 0-21, high is poor, final value) at >3 months	212 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b]	-	The mean psychological distress was 7.55	MD **1.68 lower** (2.94 lower to 0.42 lower)	MID = 0.5 SD (SMD)
Psychological distress (DASS-21 stress, 0-21, high is poor, final value) at >3 months	212 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b]	-	The mean psychological distress was 15.87	MD **4.36 lower** (6.52 lower to 2.2 lower)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with manual therapy	
Minor adverse events at ≤3 months	35 (1 RCT) follow up: 6 weeks	⊕⊕⊕◯ MODERATE [a]	Peto OR 12.18 (2.38 to 62.38)	0 per 1,000	**410 more per 1,000** (170 more to 650 more) [d]	MID (precision) = Peto OR 0.8-1.25.
Moderate/major adverse events at >3 months	105 (1 RCT) follow up: 12 months	⊕⊕⊕◯ MODERATE [b]	Peto OR 0.13 (0.00 to 6.44)	20 per 1,000	**20 fewer per 1,000** (70 fewer to 30 more) [d]	MID (precision) = Peto OR 0.8-1.25.

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c] Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
[d] Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 7: Clinical evidence summary: manual therapy and exercise versus exercise

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with exercise	Risk difference with manual therapy and exercise	
Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months	88 (1 RCT) follow up: 9 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 37.03	MD **1.42 lower** (6.12 lower to 3.28 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component, 0-100, high is good, final value) ≤3 months	88 (1 RCT) follow up: 9 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 48.92	MD **1 higher** (4.88 lower to 6.88 higher)	MID = 3 (established value)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with exercise	Risk difference with manual therapy and exercise	
Pain (VAS, 0-10, high is poor, change scores) at ≤3 months	150 (1 RCT) follow up: 9 weeks	⊕⊕⊕◯ MODERATE [a]	-	-	MD **0.6 higher** (0.43 higher to 0.77 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, NRS [different scale ranges], high is poor, final values) at ≤3 months	320 (4 RCTs) follow up: mean 8 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.78 SD lower** (1.46 lower to 0.09 higher)	MID = 0.5 SD (SMD)
Pain (VAS, 0-10, high is poor, change scores) at >3 months	318 (4 RCTs) follow up: mean 14 months	⊕◯◯◯ VERY LOW [a,b,c]	-	-	MD **0.49 lower** (0.55 lower to 1.52 higher)	MID = 0.68 (0.5 x median baseline SD)
Pain (WOMAC, 0-20, high is poor, final value) at >3 months	107 (1 RCT) follow up: 16 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean pain was 5.9	MD **1.10 lower** (2.09 lower to 0.11 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, final values) at ≤3 months	274 (3 RCTs) follow up: mean 7 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.42 SD lower** (1.05 lower to 0.21 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months	101 (1 RCT) follow up: 16 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean physical function was 19.8	MD **1.3 lower** (5.77 lower to 3.17 higher)	MID = 0.5 SD (SMD)
Psychological distress (HADS anxiety subscale, 0-21, high is poor, final value) at ≤3 months	88 (1 RCT) follow up: 9 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean psychological distress was 6.74	MD **0.43 lower** (2.5 lower to 1.64 higher)	MID = 0.5 SD (SMD)
Psychological distress (HADS depression subscale, 0-21, high is poor, final value) ≤3 months	88 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The mean psychological distress was 5.02	MD **0.19 lower** (1.89 lower to 1.51 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with exercise	Risk difference with manual therapy and exercise	
	follow up: 9 weeks					
Moderate/major adverse events at >3 months	136 (2 RCTs) follow up: mean 12 months	⨁⨁◯◯ LOW [b,d]	Peto OR 2.84 (0.39 to 20.50)	14 per 1,000	**30 more per 1,000** (40 fewer to 100 more) [e]	MID (precision) = Peto OR 0.8-1.25.

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c] Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
[d] Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
[e] Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 4: Clinical evidence summary: manual therapy and exercise versus sham therapy

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with sham therapy	Risk difference with manual therapy and exercise	
Pain (VAS, 1-10, high is poor, final value) at ≤3 months	60 (1 RCT) follow up: 8 weeks	⨁⨁⨁⨁ HIGH	-	The mean pain was 4.4	MD **2.9 lower** (3.03 lower to 2.77 lower)	MID = 0.5 SD (SMD)

Table 5: Clinical evidence summary: manual therapy and exercise versus no treatment

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with manual therapy and exercise	
Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months	86 (1 RCT) follow up: 9 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 33.82	MD **1.79 higher** (2.64 lower to 6.22 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component, 0-100, high is good, final value) ≤3 months	86 (1 RCT) follow up: 9 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 48.52	MD **1.4 higher** (4.77 lower to 7.57 higher)	MID = 3 (established value)
Quality of life (EQ-5D, 0-1, high is good, adjusted final score) at >3 months	208 (1 RCT) follow up: 24 weeks	⊕⊕⊕◯ MODERATE [a]	-	-	MD **0.11 higher** (0.04 higher to 0.18 higher)	MID = 0.03 (established value)
Pain (WOMAC, NRS, [different scale ranges], high is poor, final values) at ≤3 months	189 (2 RCTs) follow up: mean 9 weeks	⊕⊕◯◯ LOW [a,b]	-	-	SMD **0.62 SD lower** (0.92 lower to 0.33 lower)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS, 0-100, high is poor, change score and adjusted final score) at >3 months	309 (2 RCTs) follow up: mean 64 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	-	MD **7.98 lower** (22.51 lower to 6.55 higher)	MID = 5.5 (0.5 x median baseline SD)
Pain (WOMAC, 0-20, high is poor, final value) at >3 months	103 (1 RCT) follow up: 16 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean pain was 7.6	MD **2.8 lower** (3.86 lower to 1.74 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, final values) at ≤3 months	189 (2 RCTs) follow up: mean 9 weeks	⊕⊕◯◯ LOW [a,b]	-	The mean physical function was 33.0	MD **7.47 lower** (10.98 lower to 4.97 lower)	MID = 5.3 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with manual therapy and exercise	
Physical function (WOMAC, 0-100, high is poor, adjusted final values) at >3 months	311 (2 RCTs) follow up: mean 20 weeks	⨁⨁⨁◯ MODERATE [a]	-	-	SMD **0.75 SD lower** (0.98 lower to 0.52 lower)	MID = 0.5 SD (SMD)
Psychological distress (HADS anxiety subscale, 0-21, high is poor, final value) at ≤3 months	86 (1 RCT) follow up: 9 weeks	⨁⨁◯◯ LOW [a]	-	The mean psychological distress was 6.14	MD **0.17 higher** (1.87 lower to 2.21 higher)	MID = 0.5 SD (SMD)
Psychological distress (HADS depression subscale, 0-21, high is poor, final value) ≤3 months	86 (1 RCT) follow up: 9 weeks	⨁◯◯◯ VERY LOW [a,b]	-	The mean psychological distress was 5.58	MD **0.75 lower** (2.48 lower to 0.98 higher)	MID = 0.5 SD (SMD)
Moderate/major adverse events at >3 months	101 (1 RCT) follow up: 12 months	⨁⨁◯◯ LOW [b]	RR 3.06 (0.33 to 28.44)	20 per 1,000	**40 more per 1,000** (13 fewer to 538 more)	MID (precision) = RR 0.8-1.25.

[a]. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[b]. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[c]. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

1.1.7 Economic evidence

1.1.7.1 Included studies

Three health economic analyses (from four papers) with all the relevant comparisons were included in this review.[3, 72, 81, 85] These are summarised in the health economic evidence profile below (**Table 6**) and the health economic evidence tables in Appendix G.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix I.

1.1.8 Summary of included economic evidence

Table 6: Health economic evidence profile: Manual therapy

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental QALYs</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr><td>Abbott 2019[3] (Pinto 2013[81]) (New Zealand)</td><td>Partially applicable[a]</td><td>Potentially serious limitations[b]</td><td>• Within-RCT analysis (Abbott 2013[2])
• Population: People with hip or knee osteoarthritis meeting American College of Rheumatology clinical diagnostic criteria for hip or knee OA.
• Comparators:
1. Usual medical care
2. Supervised exercise plus usual care
3. Manual therapy plus usual care
4. Combination of exercise and manual therapy plus usual care
• Time horizon: 2 years</td><td colspan="4">Full incremental analysis [c][d]
<table><tr><th></th><th>Cost [e]</th><th>QALYs</th><th>Inc. Cost</th><th>Inc. QALY</th><th>Cost per QALY</th></tr><tr><td>2</td><td>£3,550</td><td>1.46</td><td colspan="3">Baseline</td></tr><tr><td>1</td><td>£3,577</td><td>1.31</td><td>-£27</td><td>-0.15</td><td>Dominated</td></tr><tr><td>4</td><td>£3,744</td><td>1.38</td><td>-£194</td><td>-0.07</td><td>Dominated</td></tr><tr><td>3</td><td>£4,602</td><td>1.39</td><td>-£1,052</td><td>-0.08</td><td>Dominated</td></tr></table>Intervention 2 dominates all other interventions.

Intervention 2 remains dominant in sensitivity analyses undertaken using complete case data only and when participants who underwent joint replacement are excluded.</td></tr>
<tr><td>Abbott 2015[1] (Pryymachenko 2021 [85])
(New Zealand)</td><td>Partially applicable[f]</td><td>Potentially serious limitations[g]</td><td>• Within-RCT analysis (Abbott 2015[1])
• Population: People aged 40 years or older with knee OA as defined by the American College of Rheumatology clinical criteria.
• Comparators:
1. Supervised exercise alone over 9 weeks
2. Supervised exercise alone over 1 year</td><td colspan="4">Full incremental analysis [b][c]
<table><tr><th></th><th>Cost [h]</th><th>QALYs</th><th>Inc. Cost</th><th>Inc. QALY</th><th>Cost per QALY</th></tr><tr><td>1</td><td>£1,297</td><td>1.26</td><td colspan="3">Baseline</td></tr><tr><td>3</td><td>£1,824</td><td>1.43</td><td>£527</td><td>0.17</td><td>£3,100</td></tr><tr><td>4</td><td>£1,829</td><td>1.33</td><td>£5</td><td>-0.10</td><td>Dominated</td></tr><tr><td>2</td><td>£1,969</td><td>1.38</td><td>£145</td><td>-0.05</td><td>Dominated</td></tr></table>Probability Intervention 3 most cost effective (£20K/£30K threshold): 79%/80% [i]</td></tr>
</table>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental QALYs	Cost effectiveness	Uncertainty
			3. Supervised exercise plus manual therapy over 9 weeks 4. Supervised exercise plus manual therapy over 1 year • Time horizon: 2 years	Results did not significantly alter when costs were increased by between 10% and 50%. Similarly, a decrease in QALYs by between 10% and 50% did not alter the probability of Intervention 3 being cost effective.			
MacPherson 2017[72] (UK)	Directly applicable	Potentially serious limitations(j)	• Probabilistic model based on three separate network meta-analyses of RCTs(k) • Cost-utility analysis (QALYs) • Population: Patients reporting pain resulting from OA of the knee. • Comparators: Manual therapy was compared to usual care(l) • Time horizon was 8 weeks	All trials: £304(m) Trials with adequate allocation concealment: £276 (m) Trials with adequate allocation concealment and an end point reported at 3-13 weeks: £277(m)	All trials: 0.008 Trials with adequate allocation concealment: 0.013 Trials with adequate allocation concealment and an end point reported at 3-13 weeks: 0.018	All trials: £38,000 Trials with adequate allocation concealment: £21,231(n) Trials with adequate allocation concealment and an end point reported at 3-13 weeks: £15,389(n)	This study analysed a variety of different intervention classes and so all reports of uncertainty were based on an analysis of all interventions and not any intervention(s) in isolation. For a summary of the analysis of uncertainty involving all interventions, see Appendix H.

Abbreviations: Inc.= incremental; NR= not reported; QALY= quality-adjusted life years; RCT= randomised controlled trial
(a) 2009 New Zealand resource use and unit costs may not reflect current UK NHS practice.
(b) Within trial analysis may not reflect full body of evidence available.
(c) Intervention number in order of least to most costly (in terms of cost)
(d) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it

would never be the most cost-effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(e) 2009 New Zealand dollars converted to UK pounds.[78]. Cost components incorporated: Medical and other healthcare consumed by participants during the trial.

(f) 2011 New Zealand resource use and unit costs may not reflect current UK NHS practice.

(g) The analysis was based on a small sample size (N=75). Thirty-five patients were lost to follow-up at two years. Within trial analysis may not reflect full body of evidence available. Source of unit costs is unclear. It is not clear what individual components make up public and private healthcare costs, and it is therefore unclear why the healthcare costs associated with Intervention 3 is substantially higher than intervention 1.

(h) 2011 New Zealand dollars converted to UK pounds.[78]. Cost components incorporated: Unit cost of physiotherapy, attendance during sessions.

(i) Figures were manually read from a graph

(j) Unit costs taken from 2011/12 may not reflect current UK NHS practice. The time horizon was only 8 weeks. Adverse events and their downstream consequences were not considered.

(k) The three network meta-analyses were: 1) an analysis involving all eligible trials; 2) an analysis including only trials with adequate allocation concealment and 3) an analysis including only trials with adequate allocation concealment and a reported end-point between 3-13 weeks. See Appendix H for all model results.

(l) The original report listed 13 interventions in total. Only those interventions that fit the protocol for manual therapy were included here. Please note intervention numbers in this profile do not match to intervention numbers in evidence table (Appendix H).

(m) 2011/12 UK pounds. Cost components incorporated: Physiotherapist's time to conduct sessions. Changes in non-treatment-related visits to GPs and specialists arising from changes to EQ-5D score

(n) In a full incremental analysis of all interventions, TENS was the most cost-effective option in the network meta-analysis of all trials with a cost per QALY of £2,690. In the other two network meta-analyses (1. only those trials with adequate allocation concealment and 2. only those trials with adequate allocation concealment and an endpoint between 3-13 weeks), acupuncture was the most cost-effective option with costs per QALYs of £13,502 and £14,275, respectively.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Resource	Unit costs (cost per hour)[(a)]	Source
Community physiotherapist including training costs (band 5/6/7)	£38/£50/£60	PSSRU 2020[39]

(a) Including qualification costs

1.1.11 Economic evidence statements

- One cost-utility analysis reported that supervised group exercise therapy alone dominated both manual therapy alone and manual therapy and exercise therapy combined. This analysis was graded as partially applicable with potentially serious limitations.
- One cost-utility analysis reported that supervised exercise alone over one year was cost effective compared with supervised exercise alone over nine weeks (ICER: £3,100). Supervised exercise alone over one year also dominated supervised exercise plus manual therapy over nine weeks and supervised exercise plus manual therapy over one year. However, manual therapy plus exercise over nine weeks was cost effective versus manual therapy alone over nine weeks. This analysis was graded as partially applicable with potentially serious limitations.
- One cost utility analysis that was based on three separate network meta-analyses reported that manual therapy was cost effective compared with usual care in only one of the three analyses (ICER; £15,389 when only trials with a low risk of bias for allocation concealment with outcomes between 3-13 weeks were included. A full incremental analysis of various non-pharmacological interventions (acupuncture, braces, heat treatment, insoles, interferential therapy, laser/light therapy, manual therapy, neuromuscular electrical stimulation, pulsed electromagnetic field, pulsed electrical stimulation, static magnets and transcutaneous electrical nerve stimulation) also reported that acupuncture was the most cost-effective strategy in two of the three network meta-analyses (£13,502 and 14,275), with transcutaneous electrical nerve stimulation the most cost-effective option in the other (£2,690). The analysis was assessed as directly applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The critical outcomes were quality of life, pain and physical function. These were considered critical due to their importance to people with osteoarthritis. The Osteoarthritis Research Society International (OARSI) consider that pain and physical function were the most important outcomes for evaluating interventions. Quality of life gives a broader perspective on the person's wellbeing, allowing for examination of the biopsychosocial impact of interventions. Psychological distress, osteoarthritis flare and minor adverse events and moderate/major adverse events were included as important outcomes.

The committee considered osteoarthritis flares to be important in the lived experience and management of osteoarthritis. However, these were also considered difficult to measure with no clear consensus on their definition. The Flares in OA OMERACT working group have proposed an initial definition and domains of OA flares through a consensus exercise; "it is a

transient state, different from the usual state of the condition, with a duration of a few days, characterized by onset, worsening of pain, swelling, stiffness, impact on sleep, activity, functioning, and psychological aspects that can resolve spontaneously or lead to a need to adjust therapy.“. However, this has been considered to have limitations and has not been widely adopted. Therefore, the committee included the outcome accepting any reasonable definition provided by any studies discussing the event.

Mortality was included as a treatment adverse event rather than as a discreet outcome and categorised as an important outcome. Osteoarthritis as a disease process is not considered to cause mortality by itself and mortality is an uncommon outcome from osteoarthritis interventions.

There was evidence available for all outcomes apart from osteoarthritis flares. However, while some data was available, there was only limited evidence available for psychological distress and adverse events throughout the literature.

1.1.12.2 The quality of the evidence

Fifteen studies were included in this review. The comparisons where evidence was present included:

- Manual therapy compared to sham therapy
- Manual therapy compared to no treatment
- Manual therapy and exercise compared to exercise
- Manual therapy and exercise compared to sham therapy
- Manual therapy and exercise compared to no treatment

The evidence varied from high to very low quality due to a mixture of risk of bias, imprecision and inconsistency. The committee concluded that the amount of evidence had increased since the previous version of the guideline. However, the quality of that evidence had not improved. While some studies had more participants than previous studies, the blinding was often inadequate and allocation concealment was not well reported. Inconsistency led to issues in comparisons where more evidence was available, with some studies showing significantly larger benefits than others. The reasons for this heterogeneity could not be explained by subgroup analyses agreed in the protocol.

Manual therapy compared to sham therapy

The evidence for this comparison ranged from moderate to very low quality due to a mixture of imprecision and inconsistency, where heterogeneity could not be resolved by subgroup analysis. Risk of bias was mostly due to a mixture of selection (due to inadequate reporting of allocation concealment).

Manual therapy compared to no treatment

The evidence for this comparison ranged from moderate to very low quality due to a mixture of risk of bias, imprecision and inconsistency, where heterogeneity could not be resolved by subgroup analysis. Risk of bias was mostly due to a mixture of selection (due to inadequate reporting of allocation concealment and/or differences in baseline values between study arms) and performance bias (due to inadequate blinding of participants and outcome assessors).

Manual therapy and exercise compared to exercise

The evidence for this comparison ranged from moderate to very low quality due to a mixture of risk of bias, imprecision and inconsistency, where heterogeneity could not be resolved by

subgroup analysis. Risk of bias was mostly due to a mixture of selection (due to inadequate reporting of allocation concealment) and performance bias (due to inadequate blinding of participants and outcome assessors).

Manual therapy and exercise compared to sham therapy

The evidence for this comparison was reported in one study with 60 participants and included one outcome, pain at less than or equal to 3 months. The quality of this outcome was high.

Manual therapy and exercise compared to no treatment

The evidence for this comparison ranged from moderate to very low quality due to a mixture of risk of bias, imprecision and inconsistency, where heterogeneity could not be resolved by subgroup analysis. Risk of bias was mostly due to a mixture of selection (due to inadequate reporting of allocation concealment), performance (due to inadequate blinding of participants and outcome assessors) or attrition bias (due to incomplete outcome data being available).

1.1.12.3 Benefits and harms

Key uncertainties

The committee acknowledged that while there was more evidence then when the review was conducted in the previous version of the guideline, the evidence was limited due to higher risk of bias in included studies and the presence of imprecision. This was linked to the small number of participants in studies. The committee concluded that the limitations in study design made it difficult to determine the effect of manual therapy.

The committee discussed that generally the adverse events data for these trials was limited as this was generally found in small studies with a short follow up time and so it is unclear whether this is representative of the events expected to be seen in real life practice. Given this, the committee considered the evidence for serious adverse events to be unclear throughout the review reflecting this in their weighting of findings while making recommendations. The committee noted throughout the evidence that the number of adverse events was often low and where events were reported they were transient in nature (such as increased pain). Given this, while the committee acknowledged where clinically important differences were highlighted in the evidence, but also considered the nature and true number of these events.

Manual therapy compared to sham therapy

Evidence from this comparison was reported in studies where at most 222 participants were present in the outcomes. The evidence showed a clinically important benefit in quality of life at >3 months for the SF-36 mental component only, pain at ≤3 and >3 months and physical function at ≤3 months. No clinically important difference was seen in quality of life at ≤3 months for the SF-36 mental component only, quality of life at >3 months for the SF-36 physical component and physical function at >3 months. A clinically important harm was seen in quality of life at ≤3 months for the SF-36 physical component only.

Manual therapy compared to no treatment

Evidence for this comparison included more studies where at most 331 participants were present in the outcomes. The evidence showed clinically important benefits in quality of life at >3 months, pain at ≤3 and >3 months and physical function at ≤3 and >3 months. There were unclear effects where some outcomes showed clinically important benefits while others showed no clinically important difference in quality of life at ≤3 months and psychological distress at ≤3 and >3 months. No clinically important difference in moderate/major adverse

events at >3 months was seen. However, a clinically important harm in minor adverse events at ≤3 months was seen (based on one small study with 35 participants).

Manual therapy and exercise compared to exercise

Evidence for this comparison was reported in a larger number of studies. However, the number of participants included in an outcome was at most 320 participants. The evidence showed an unclear effect on pain at ≤3 months. One outcome (including a change score) including one study with 150 participants but of moderate quality showed a clinically important benefit of exercise alone, while another outcome (including final values) including four studies with 320 participants but of very low quality showed clinically important benefits of manual therapy and exercise. Otherwise no clinically important differences were seen in quality of life at ≤3 months, pain at >3 months, physical function at ≤3 and >3 months, psychological distress at ≤3 months and moderate/major adverse events at >3 months.

Manual therapy and exercise compared to sham therapy

Evidence for this comparison was reported in one study with 60 participants. The only outcome reported was pain at ≤3 months which showed a clinically important benefit of manual therapy and exercise. This was based on high quality evidence. The committee acknowledged that the evidence for this comparison was difficult to interpret due to the potential effect that exercise alone may have on the result.

Manual therapy and exercise compared to no treatment

Evidence for this comparison was reported in more studies. However, the number of participants included in an outcome was at most 311 participants. The evidence showed clinically important benefits of manual therapy and exercise in quality of life at >3 months, pain at ≤3 and >3 months and physical function at >3 months. However, the evidence showed no clinically important differences in quality of life at ≤3 months, physical function at ≤3 months, psychological distress at ≤3 months and moderate/major adverse events at >3 months. The committee acknowledged that the evidence for this comparison was difficult to interpret due to the potential effect that exercise alone may have on the result.

Weighing up the clinical benefits and harms

On considering this evidence, the committee acknowledged that while there were some benefits due to manual therapy this was often in outcomes that were imprecise or heterogenous with inconsistency that could not be resolved by subgroup analysis. Due to the nature of this, the committee concluded that there was insufficient evidence to indicate a benefit from manual therapy alone. However, there was evidence of benefit for manual therapy when combined with exercise that may the benefit from exercise alone in pain The committee acknowledged the uncertainty in the outcomes for this, but overall agreed that manual therapy when combined with exercise could be considered for people with osteoarthritis. This may be appropriate for people who are finding it difficult to start exercise alone.

Given this the committee recommending that manual therapy should only be considered for people with knee and hip osteoarthritis, delivered in combination with exercise and that people should be informed that there is insufficient evidence for manual therapy alone. The committee found that the majority of evidence was at less than 3 months with the average amount of time that manual therapy was provided for being seven weeks. Given this, the committee agreed that manual therapy should be provided in the short term to help people to start exercise if they were finding this difficult without additional intervention. However, they recommended that further research was required to understand this more and provide evidence for joint sites other than hip and knee osteoarthritis (see research recommendations).

1.1.12.4 Cost effectiveness and resource use

Manual therapy may be delivered by physiotherapists, chiropractors or osteopaths in the NHS.

Three economic evaluations were identified in the review. One economic evaluation showed that for people with hip and knee osteoarthritis, supervised group exercise therapy alone dominated both manual therapy alone and manual and exercise therapy combined.

A second economic evaluation took a UK perspective and was based on three separate network meta-analyses of randomised controlled trials (RCTs); one analyses was based on all eligible trials, one was confined to only those trials that utilised adequate allocation concealment and the final analyses further limited the trials to include those with a adequate allocation concealment and an end point reported at 3-13 weeks. QALYs were calculated by mapping from various measures to EQ-5D and then pooling the results to give an overall estimate. It was deemed to be directly applicable. The model time horizon was relatively short at 8 weeks. The unit costs were taken from 2011/12 and were therefore unlikely to be representative of current NHS practice. For these reasons, it was graded as having potentially serious limitations.

The analysis compared various non-pharmacological interventions to usual care (acupuncture, braces, heat treatment, insoles, interferential therapy, laser/light therapy, manual therapy, neuromuscular electrical stimulation (NMES), pulsed electromagnetic field (PEMF), pulsed electrical stimulation (PES), static magnets and transcutaneous electrical nerve stimulation (TENS)). Manual therapy was not cost effective versus usual care at a cost per QALY gained threshold of £20,000 in two of the three analyses; the analysis that considered all trials as well as the analysis that limited to trials to those with suitable allocation concealment. In the analysis that confined trials to those with suitable allocation concealment as well as an end point at 3-13 weeks, manual therapy was cost effective versus usual care with a cost per QALY reported of £15,389.

In a full incremental analysis, TENS was the most cost-effective option in an analysis of all trials with a cost per QALY gained of £2,690. However, acupuncture was the most cost-effective option in an analysis of trials with a low risk of bias for allocation concealment and trials with a low risk of bias for allocation concealment with outcomes between 3-13 weeks with costs per QALY gained of £13,502 and £14,275, respectively.

The final economic evaluation had a New Zealand perspective. The analysis was based on a single randomised controlled trial of 75 participants with four comparators: supervised exercise alone over nine weeks, supervised exercise alone over one year, supervised exercise plus manual therapy over nine weeks and supervised exercise plus manual therapy over one year. The sources of costs that were used during the analysis were unclear. This evaluation was graded as partially applicable with potentially serious limitations. The most cost-effective intervention was supervised exercise alone over nine weeks with a cost per QALY gained of £3,100 versus supervised exercise alone over nine weeks. This option also dominated both interventions with manual therapy included, being cheaper and more effective. However, manual therapy plus exercise delivered over nine weeks was cost effective versus manual therapy alone over nine weeks.

The cost effectiveness evidence from these three studies was mixed overall. The committee concluded that manual therapy could be cost effective as an adjunct to exercise but not by itself. It therefore recommended that manual therapy be considered as an adjunct to therapeutic exercise in people with osteoarthritis of the hip, knee, or hand.

1.1.12.5 Other factors the committee took into account

The committee also considered the delivery of manual therapy. Manual therapy would be delivered by healthcare professionals including physiotherapists and other allied professionals such as chiropractors and osteopaths. Treatment is typically individual and

delivered face to face. The committee acknowledged that this may be challenging in current practice due to changes following the COVID-19 pandemic. The committee noted that some evidence reported people being taught to deliver manual therapy to themselves, which may be a way to resolve some of the challenges from this. However, further research would be required to ensure that self-administered manual therapy is as effective as manual therapy delivered by a healthcare professional. This was incorporated in research recommendation.

The committee noted that the research identified does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone. With this in mind the committee subgrouped their research recommendation by these protected characteristics where appropriate while suggesting that people from each group should be included in the research to ensure that it is applicable to the entire population.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.6 to 1.3.7 and the research recommendation on manual therapy. Other evidence supporting these recommendations can be found in evidence review E.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for manual therapy

ID	Field	Content
0.	PROSPERO registration number	N/A
1.	Review title	What is the clinical and cost-effectiveness of manual therapy for the management of osteoarthritis?
2.	Review question	3.3 What is the clinical and cost-effectiveness of manual therapy for the management of osteoarthritis?
3.	Objective	To assess the clinical and cost-effectiveness of manual therapy (including passive and active mobilisation) in the management of osteoarthritis.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded

		Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Osteoarthritis (of any joint) in adults (defined as a clinical diagnosis of osteoarthritis with or without imaging)
6.	Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Exclusion: • Children (age ≤16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy).
7.	Intervention/Exposure/Test	Interventions (minimum duration 1 week): • Manual therapy alone • Manual therapy and exercise combined Manual therapy will be pooled in the analysis and interventions may include: • Manipulation and/or mobilisation (joint or neurodynamic mobilisation, traction)

		• Passive stretching • Soft tissue techniques • Acupressure/ trigger point therapy • Combined active and passive manual therapy

8.	Comparator/Reference standard/Confounding factors	• Sham manual therapy
		• No manual therapy intervention (including either):
		  ○ Manual therapy versus no treatment*
		  ○ Manual therapy plus additional treatment versus additional treatment alone**
		**No treatment defined as either (1) doing nothing or (2) very low intensity intervention such as advice*
		***Inclusion of studies where additional treatment is the same in each arm will be assessed on a case by case basis. Studies including high intensity additional treatment may not be included due to the risk that treatment could have an interaction with the intervention of interest and mask the true treatment effect.*
		• Exercise (Compared to manual therapy and exercise only)

9.	Types of study to be included	• Systematic reviews of RCTs • Parallel RCTs
10.	Other exclusion criteria	• Self administered manual therapy • Manual therapy involving needles • Non-English language studies • Non-randomised/observational studies Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A

12.	Primary outcomes (critical outcomes)	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] The COMET database was searched and several core outcome sets were identified for specific sites of osteoarthritis (including hand, knee and hip). The committee took these into account when defining outcomes: https://onlinelibrary.wiley.com/doi/full/10.1002/acr.22868 https://www.ncbi.nlm.nih.gov/pubmed/26136489 https://www.ncbi.nlm.nih.gov/pubmed/30647185 The committee did not include stiffness or global scores as Delphi discussions by the OMERACT group have found these to not be as important to people with osteoarthritis or clinicians. The outcomes included were universal for all groups allowing for broader comparisons.
13.	Secondary outcomes (important outcomes)	• Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [validated patient-reported outcomes, continuous data prioritised] • Minor adverse events [dichotomous] • Moderate/major adverse events [dichotomous]
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.

		Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual For intervention reviews the following checklists will be used according to the study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/

		• Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified. Heterogeneity between studies in the effect measures will be assessed using the I^2 statistic and visual inspection. We will consider an I^2 value great than 50% as indicative of substantial heterogeneity. If significant heterogeneity is identified during meta-analysis then subgroup analysis, using subgroups predefined by the GC, will take place. If this does not explain the heterogeneity, the results will be presented using a random-effects model.	
17.	Analysis of sub-groups	Subgroup analysis to be conducted if heterogeneity in the meta-analysis is present: • Site of osteoarthritis • By type of manual therapy intervention: o Mobilisation/manipulation (joint or neurodynamic) o Passive stretching o Soft tissue techniques (including massage, acupressure) • Age (≤/>75 years) • Multimorbidity • Diagnosis with or without imaging	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	23/08/2019		
22.	Anticipated completion date	25/08/2021		
23.	Stage of review at time of this submission	Review stage	Started	
		Preliminary searches	☑	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address]		

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Rebecca Boffa [Senior systematic reviewer] George Wood [Systematic reviewer] Emma Cowles [Senior health economist] Joseph Runicles [Information specialist] Amber Hernaman [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10127

29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Active mobilisation; Active stretching; Adults; Intervention; Manual therapy; Non-Pharmacological; Osteoarthritis; Passive stretching	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 7: Health economic review protocol

Review question	All questions – health economic evidence

Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2005 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[75] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion**

	The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B – Literature search strategies

- What is the clinical and cost-effectiveness of manual therapy for the management of osteoarthritis?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[75]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using an Osteoarthritis population. All results were then sifted for each question. Search filters were applied to the search where appropriate.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 17 November 2021	Randomised controlled trials Systematic review studies Exclusions (animals studies, letters, comments)
Embase (OVID)	1974 – 17 November 2021	Randomised controlled trials Systematic review studies Exclusions (animals studies, letters, comments)
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 11 of 12 CENTRAL to 2021 Issue 11 of 12	None

Medline (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14

16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	randomized controlled trial.pt.
28.	controlled clinical trial.pt.
29.	randomi#ed.ti,ab.
30.	placebo.ab.
31.	randomly.ti,ab.
32.	Clinical Trials as topic.sh.
33.	trial.ti.
34.	or/27-33
35.	Meta-Analysis/
36.	exp Meta-Analysis as Topic/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	26 and (34 or 45)

Embase (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.

12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 not English language
25.	random*.ti,ab.
26.	factorial*.ti,ab.
27.	(crossover* or cross over*).ti,ab.
28.	((doubl* or singl*) adj blind*).ti,ab.
29.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
30.	crossover procedure/
31.	single blind procedure/
32.	randomized controlled trial/
33.	double blind procedure/
34.	or/25-33
35.	systematic review/
36.	meta-analysis/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	24 and (34 or 45)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Osteoarthritis] explode all trees
#2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*):ti,ab
#3.	(degenerative near/2 arthritis):ti,ab
#4.	coxarthrosis:ti,ab
#5.	gonarthrosis:ti,ab

#6.	(or #1-#5)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updates after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies. Searches for quality of life studies were run for general information.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1 January 2014 – 17 November 2021	Health economics studies Quality of life studies Exclusions (animals studies, letters, comments)
Embase	1 January 2014 – 17 November 2021	Health economics studies Quality of life studies Exclusions (animals studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16

18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.

57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp osteoarthritis/
2.	(osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3.	(degenerative adj2 arthritis).ti,ab.
4.	coxarthrosis.ti,ab.
5.	gonarthrosis.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.

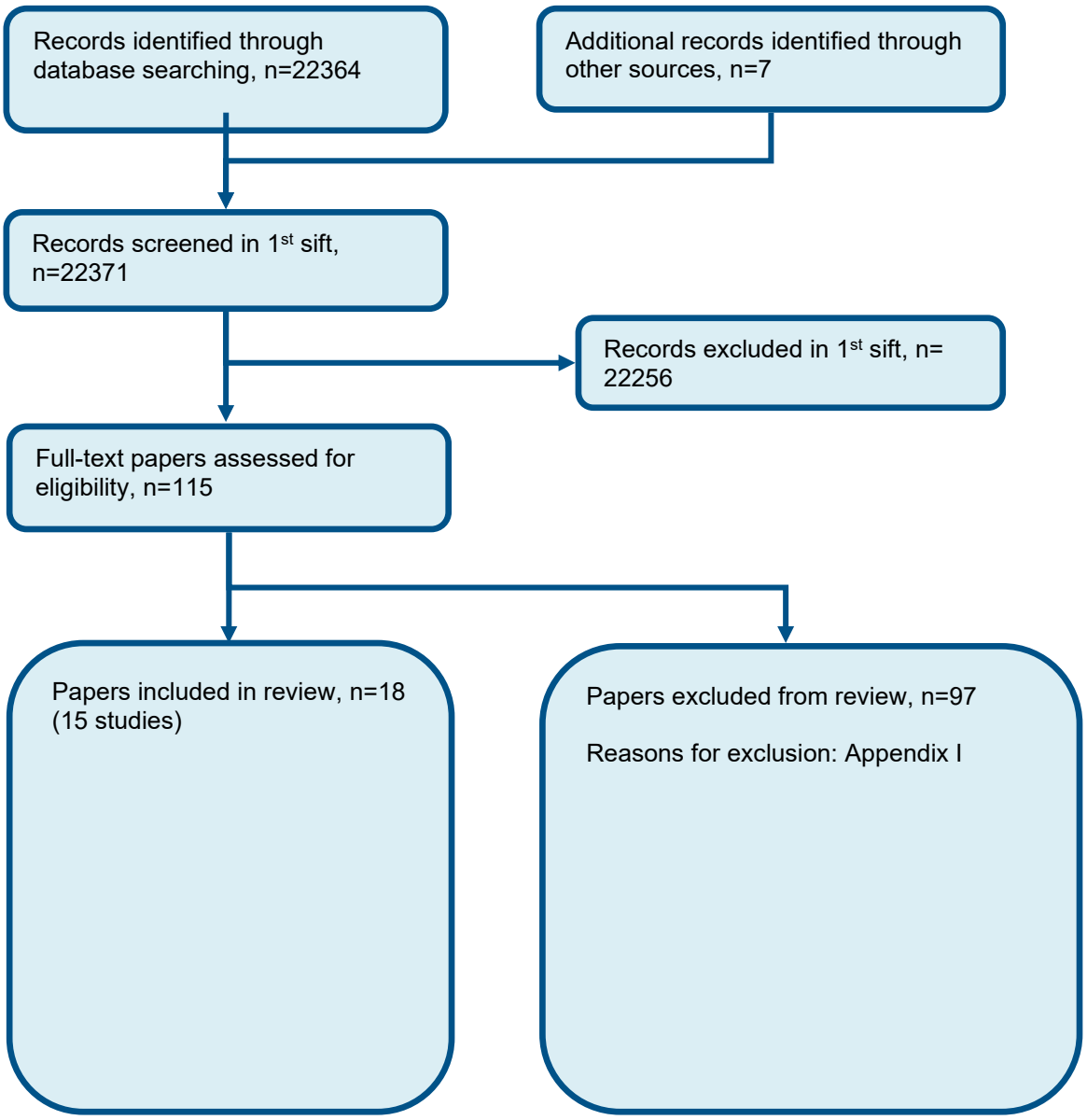
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	"quality of life index"/
41.	short form 12/ or short form 20/ or short form 36/ or short form 8/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.
44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.
54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/39-59
61.	24 and (38 or 60)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Osteoarthritis EXPLODE ALL TREES
#2.	((osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*))
#3.	((degenerative adj2 arthritis))
#4.	(coxarthrosis)
#5.	(gonarthrosis)
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(#6) IN NHSEED
#8.	(#6) IN HTA

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of manual therapy for Osteoarthritis



Appendix D – Effectiveness evidence

Study (subsidiary papers)	Abbott 2013[2] (Abbott 2019[3])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=206)
Countries and setting	Conducted in New Zealand; Setting: Physiotherapy centre.
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: American College of Rheumatology criteria for hip or knee OA
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Meet clinical criteria for diagnosis of OA of the hip or knee established by the American College of Rheumatology.
Exclusion criteria	Rheumatoid arthritis; previous knee or hip joint replacement surgery of the affected joint; any other surgical procedure on the lower limbs in the previous 6 months; surgical procedure on the lower limbs planned in the next 6 months; initiation of opioid analgesia or corticosteroid or analgesic injection intervention for hip or knee pain within the previous 30 days; physical impairments unrelated to the hip or knee which would prevent safe participation in exercise, manual therapy, walking or stationary cycling; inability to comprehend and complete study assessments or comply with study instructions; or stated inability to attend or complete the proposed course of intervention and follow-up schedule.
Recruitment/selection of patients	General practitioner referral of patients with hip or knee OA; patients referred by their GP to a hospital orthopaedic outpatient clinic for an orthopaedic consultation to consider hip or knee joint replacement surgery.
Age, gender and ethnicity	Age - Mean (SD): 67.3 (10.2) usual care plus manual therapy; 66.1 (10.7) usual care control . Gender (M:F): 92/114. Ethnicity: Not reported
Further population details	1. Age: ≤ 75 years 2. Diagnosis with or without imaging: Diagnosis without imaging 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Mixed
Extra comments	Severity: pain intensity score 4.2 (2.3) in the usual care plus manual therapy group and 3.1 (2.0) in the usual care group.

	Duration of symptoms (duration since first diagnosis of OA (years) 2.5 (1.4) for usual care plus manual therapy group and 2.8 (1.3) for usual care group.
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Manual therapy alone - Mixed therapies. Usual care plus manual therapy: manual therapy consisted of procedures intended to modify the quality and range of motion of the target joint and associated soft tissue structures. Additional manual therapy interventions were prescribed individually for each participant randomised to this intervention on the basis of the physical examination findings, from a limited list of interventions. Also a home programme of joint range of motion activities to be completed three times per week. . Duration 9 treatment sessions of approximately 50 minutes, 7 over 9 weeks and 2 booster sessions at week 16. Concurrent medication/care: Not stated.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Mixed (n=51) Intervention 2: No manual therapy - No treatment. Usual care offered by their own GP and other healthcare providers. . Duration 9 weeks. Concurrent medication/care: Not stated. . Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable (n=50) Intervention 3: Manual therapy and exercise combined - Combined active and passive manual therapy and exercise. Same manual therapy approach explained previously, with an exercise program consisting of a multi-modal supervised programme of warm-up/aerobic, muscle strengthening, muscle stretching and neuromuscular control exercises. Additional exercises were prescribed individually for each participant on the basis of the physical examination findings. In addition participants completed the home exercise programme prescribed to all participants.. Duration 9 treatment sessions of approximately 50 minutes, 7 over 9 weeks and 2 booster sessions at week 16. Concurrent medication/care: Not stated.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Mixed (n=51) Intervention 4: Exercise - Exercise (compared to manual therapy and exercise only). Exercise programme only with the same usual care as all other treatments. Duration 9 weeks. Concurrent medication/care: Not stated.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable

Funding	Academic or government funding (Research contracts from the Health Research Council of NEw Zealand and the New Zealand Lottery Grants Board.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED THERAPIES versus NO TREATMENT

Protocol outcome 1: Pain at > 3 months
- Actual outcome: Pain intensity score (range 0-10, lower scores better) at 2 year; Group 1: mean -1.65 (SD 2.39575); n=54, Group 2: mean -1.01 (SD 2.345); n=51; Pain intensity score 0-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain intensity score range: 4.2 (2.3) usual care + manual therapy versus 3.1 (2.0) usual care group ; Group 1 Number missing: 4; Group 2 Number missing: 4

Protocol outcome 2: Moderate/major adverse events at > 3 months
- Actual outcome: Adverse events (in this instance death, which was described as non-trial related). at 1 year; Group 1: 1/54, Group 2: 0/51
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINED ACTIVE AND PASSIVE MANUAL THERAPY AND EXERCISE versus NO TREATMENT

Protocol outcome 1: Pain at > 3 months
- Actual outcome: Pain intensity score (range 0-10, lower scores better) at 2 year; Group 1: mean -1.78 (SD 2.44); n=50, Group 2: mean -1.01 (SD 2.37); n=51; VAS 0-10 Top=High is poor outcome; Comments: Reported change scores and 95% confidence intervals. Converted into SD. Reported exercise + manual therapy: -1.78 (-2.45 to -1.10). Reported no treatment: -1.01 (-1.66 to -0.36). Baseline exercise + manual therapy: 4.0 (2.1). Baseline no treatment: 3.1 (2.0).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in pain at baseline; Group 1 Number missing: 7, Reason: 1 deceased, 1 deteriorating eyesight, 2 too busy, 1 ill health (complications following arthroplasty), 2 withdrew; Group 2 Number missing: 4, Reason: 1 deceased, 2 ill health, 1 ill health of spouse

Protocol outcome 2: Moderate/major adverse events at > 3 months
- Actual outcome: Adverse events at 1 year; Group 1: 3/50, Group 2: 1/51; Comments: Exercise and manual care: 1 inguinal hernia, 1 post-operative complication following total knee arthroplasty, 1 non-trial related death. No treatment: 1 non-trial related death.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 1 deceased, 1 deteriorating eyesight, 2 too busy, 1 ill health, complications following arthroplasty; Group 2 Number missing: 4, Reason: 1 deceased, 2 ill health, 1 ill health of spouse

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINED ACTIVE AND PASSIVE MANUAL THERAPY AND EXERCISE

versus EXERCISE (COMPARED TO MANUAL THERAPY AND EXERCISE ONLY) Protocol outcome 1: Pain at > 3 months - Actual outcome: Pain intensity score (range 0-10, lower scores better) at 2 year; Group 1: mean -1.78 (SD 2.44); n=50, Group 2: mean -1.92 (SD 2.3); n=51; VAS 0-10 Top=High is poor outcome; Comments: Reported change scores and 95% confidence intervals. Converted into SD. Reported exercise + manual therapy: -1.78 (-2.45 to -1.10). Reported exercise: -1.92 (-2.55 to -1.29). Baseline exercise + manual therapy: 4.0 (2.1). Baseline exercise: 3.5 (2.0). Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: 1 deceased, 1 deteriorating eyesight, 2 too busy, 1 ill health (complications following arthroplasty), 2 withdrew; Group 2 Number missing: 4, Reason: 1 dementia, 1 personal reasons, 2 withdrew Protocol outcome 2: Moderate/major adverse events at > 3 months - Actual outcome: Adverse events at 1 year; Group 1: 3/50, Group 2: 0/51; Comments: Exercise and manual care: 1 inguinal hernia, 1 post-operative complication following total knee arthroplasty, 1 non-trial related death Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 1 deceased, 1 deteriorating eyesight, 2 too busy, 1 ill health, complications following arthroplasty; Group 2 Number missing: 2, Reason: 1 dementia, 1 personal reasons	
Protocol outcomes not reported by the study	Health related quality of life at ≤/=3 months; Health related quality of life at > 3 months; Physical function at ≤/=3 months; Physical function at > 3 months; Pain at ≤/=3 months; Psychological distress at ≤/=3 months; Psychological distress at > 3 months; Osteoarthritis flares at ≤/=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at ≤/=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at ≤/=3 months

Study	Abbott 2015[1] (Pryymachenko 2021[85])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in New Zealand; Setting: Dunedin Hospital, New Zealand.
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: American College of Rheumatology clinical criteria for a diagnosis of knee OA.
Stratum	Overall:
Subgroup analysis within study	Not applicable
Inclusion criteria	40 years of age or older and meet the American College of Rheumatology clinical criteria for a diagnosis of knee OA.
Exclusion criteria	Rheumatoid arthritis; previous knee or hip joint replacement surgery of the affected joint; any other surgical procedure on the lower limbs in the previous 6 months; surgical procedure on the lower limbs planned in the next 6 months; initiation of opioid analgesia or corticosteroid or analgesic injection intervention for hip or knee pain within the previous 30 days; physical impairments unrelated to the hip or knee that would prevent safe participation in exercise, manual therapy, walking or stationary cycling; inability to comprehend and complete study assessments or comply with study instructions; or stated inability to attend or complete the proposed course of intervention and follow-up schedule.
Recruitment/selection of patients	Recruited in Dunedin, New Zealand by 3 sources: patients presenting to physical therapy with knee pain; patients referred for orthopaedic consultation for knee OA but not eligible for joint replacement surgery, and people with knee OA on their clinical trials mailing list.
Age, gender and ethnicity	Age - Mean (SD): Manual therapy + exercise group: 61(12); exercise group: 64(10). Gender (M:F): 29:46. Ethnicity: Not stated.
Further population details	1. Age: ≤ 75 years 2. Diagnosis with or without imaging: Diagnosis without imaging 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Severity: pain intensity score (VAS 0-10) 2.8 (1.9); 2.1 (1.2) Duration of symptoms: ≤ 1 year: 4 versus 3; 1-2 years: 4 versus 2; 3-5 years: 1 versus 3; 5-10 years: 2 versus 9; > 10 years: 7 versus 2.

Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Manual therapy and exercise combined - Combined active and passive manual therapy and exercise. Mandatory interventions: Knee flexion: nonthrust physiologic motion; anteroposterior-directed force to the tibia, tibiofemoral joint: nonthrust; knee extension: nonthrust physiologic motion; posteroanterior-directed force to the tibia, tibiofemoral joint: nonthrust; patellar gliding force: nonthrust; manual stretch to quadriceps, hamstrings, triceps surae muscles; soft tissue manipulation: quadriceps and peripatellar connective tissue, hamstrings, hip adductors, and triceps surae muscles. Secondary (nonmandatory) interventions prescribed when indicated by assessment findings: long axis hip distraction with thrust; lateral hip distraction: nonthrust; anteroposterior-directed force to proximal femur: nonthrust; posteroanterior-directed force to proximal femur: nonthrust; medial hip rotation: nonthrust; soft tissue manipulation to hip and thigh musculature and fascia; manual stretches to connective tissue of hip and thigh; ankle and talocalcaneal joint distraction: thrust or nonthrust; ankel talocrural anteroposterior-directed force: nonthrust; anteroposterior-directed force to distal fibula ,tibiofibular joint: nonthrust; soft tissue manipulation: ankle plantar flexor muscle group; lumbopelvic rotation: thrust manipulation. Home program of reinforcing activities: prescribe up to 6 range-of-motion activities to reinforce clinic interventions. Exercise (mandatory interventions): aerobic exercise: up to 10 minutes, cycle or walk; strengthening: 3 sets of 10 repetitions of knee extension, hip extension, knee flexion. Resistance adjusted as appropriate; stretching: 60-second passive stretch of knee flexors, knee extensors, ankle plantar flexors; Neuromuscular coordination control exercises: 3 sets of 2 minutes of (choose from) standing weight shifting, standing balance on uneven surfaces, sidestepping, forward/backward and shuttle walking drills, stair walking. Secondary (nonmandatory) interventions, prescribed when indicated by assessment findings: ankle planter flexor strengthening, hip abductor strengthening, hip lateral rotator strengthening, hip flexor and knee extensor stretching, trunk muscle strengthening. Home exercise program: prescribe up to 6 of the above activities to reinforce clinic interventions.. Duration 12 sessions of 30-45 minutes manual therapy; 45 minutes exercise. . Concurrent medication/care: Not stated. Further details: 1. Type of manual intervention: Mixed

	(n=19) Intervention 2: Exercise - Exercise (compared to manual therapy and exercise only). Exercise (mandatory interventions): aerobic exercise: up to 10 minutes, cycle or walk; strengthening: 3 sets of 10 repetitions of knee extension, hip extension, knee flexion. Resistance adjusted as appropriate; stretching: 60-second passive stretch of knee flexors, knee extensors, ankle plantar flexors; Neuromuscular coordination control exercises: 3 sets of 2 minutes of (choose from) standing weight shifting, standing balance on uneven surfaces, sidestepping, forward/backward and shuttle walking drills, stair walking. Secondary (nonmandatory) interventions, prescribed when indicated by assessment findings: ankle plantor flexor strengthening, hip abductor strengthening, hip lateral rotator strengthening, hip flexor and knee extensor stretching, trunk muscle strengthening. Home exercise program: prescribe up to 6 of the above activities to reinforce clinic interventions.. Duration 45 minutes exercise. . Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	Academic or government funding (New Zealand lottery grants Board, the New Zealand Society of Physiotherapists Scholarships Trust, the Health Research Council of New Zealand, and a University of Otago Research grant.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINED ACTIVE AND PASSIVE MANUAL THERAPY AND EXERCISE versus EXERCISE (COMPARED TO MANUAL THERAPY AND EXERCISE ONLY)

Protocol outcome 1: Pain at > 3 months

- Actual outcome: Pain intensity score at 2 year ; MD; -1.56 (95%CI -3.48 to 0.35) VAS 0-10 Top=High is poor outcome, Comments: Adjusted for age, sex, baseline BMI, numerical pain score, duration since first diagnosis, mental health and baseline outcomes.

Baseline values: manual therapy plus exercise: 2.8 (1.9), exercise: 2.1 (1.2);

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: Too busy (3), no contact (2), declined (2); Group 2 Number missing: 7, Reason: Ill health (1), too busy (2), no contact (2), unknown (1), declined (1)

Protocol outcome 2: Moderate/major adverse events at > 3 months

- Actual outcome: Adverse events (possible trial-related hip pain) at 1 year ; Group 1: 0/17, Group 2: 1/18; Comments: Possibly trial-related hip pain associated with exercise.

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Time commitments; Group 2 Number missing: 1, Reason: Unable to follow up	
Protocol outcomes not reported by the study	Health related quality of life at ≤/=3 months; Health related quality of life at > 3 months; Physical function at ≤/=3 months; Physical function at > 3 months; Pain at ≤/=3 months; Psychological distress at ≤/=3 months; Psychological distress at > 3 months; Osteoarthritis flares at ≤/=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at ≤/=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at ≤/=3 months

Study	Akbarnezhad 2019[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=51)
Countries and setting	Conducted in Iran; Setting: Nursing homes.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed by a rheumatologist and based on x-ray.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>60 years old; diagnosed with grade II to III OA according to Kellgren-Lawrence grading system in one or both knees by a rheumatologist and based on x-ray; not having a severe pain in the afflicted knee (<90% of maximum pain according to VAS); no pertinent knee surgery history (replacement, reconstructive); acceptable cognitive health status (score of 7 or higher according to Abbreviated Mental Test); no health situation contradicting with acupressure (i.e. open wounds, cancer); no severe symptoms of psychological distress; no use of narcotic drugs; no other chronic diseases in a critical stage (i.e. insulin dependent diabetes, lupus); and no injection of analgesics into the afflicted knee in the past 40 days or having plan to inject during the study.
Exclusion criteria	Withdrawing from the study; leaving the nursing home; death or intensification of symptoms so that hospitalisation was needed; development of acute diseases or any intervening conditions; injecting analgesics medications to the afflicted knee during the study.
Recruitment/selection of patients	Recruited from nursing homes.
Age, gender and ethnicity	Age - Other: Acupressure group: 60-70 (4), 71-80 (8), 82-90 (2), 91-95 (0); sham group: 60-70 (4), 71-80 (6), 82-90 (4), 91-95 (0); usual care group: 60-70 (6), 71-80 (8), 82-90 (5), 91-95 (2);. Gender (M:F): Acupressure group: 6M/8F; sham group: 5M/9F; usual care group: 8M/13F. Ethnicity: Not reported
Further population details	1. Age: Systematic review: mixed (inclusion criteria was >60 years). 2. Diagnosis with or without imaging: Diagnosis with imaging (x-ray imaging). 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Duration (years): acupressure group: 1-5(6), 5-10(2), 10-15(4), <15 (2); sham group: 1-5(3), 5-10(6), 10-15(3), <15 (2) usual care group: 1-5(8), 5-10(8), 10-15(1), <15 (4)

	Severity (WOMAC pain): acupressure group: 9.14 (2.31), sham group: 9.86 (2.71), usual care group: 2.78 (2.78)
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Manual therapy alone - Acupressure/trigger point therapy. An acupressure protocol (includes information about different effective knee acupoints, several strategies of acupuncture, caution notes etc.), was developed by the researcher according to related literature. This protocol was reviewed further by members of the research team, the nursing home authorities and Tehran Welfare Organisation experts. The executive researcher was trained for a month under the supervision of a physiotherapist who was qualified in the acupuncture and acupressure therapy. In the acupressure group, the intervention included one minute of deep pressure on one of eight selected acupoints on the knee . Participants were asked to wear comfortable clothes for sessions and breathe deeply during the intervention. The intervention lasted for 10 continuous 15 minute sessions for 3-4 weeks (acupressure group in the odds and placebo group in even days of the week).. Duration 3-4 weeks. Concurrent medication/care: Not reported.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Soft tissue techniques (acupressure). (n=15) Intervention 2: Sham manual therapy. Intervention for the placebo group included manipulation of eight fake points that were selected away from the real acupoint and only gentle touching was done instead of required pressure. The intervention lasted for 10 continuous 15 minute sessions for 3-4 weeks (acupressure group in the odds and placebo group in even days of the week).. Duration 3-4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable (n=21) Intervention 3: No manual therapy - No treatment. The control group received no intervention except the nursing home routine care.. Duration 3-4 weeks. Concurrent medication/care: Not reported.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY versus SHAM MANUAL THERAPY

Protocol outcome 1: Physical function at </=3 months

- Actual outcome: WOMAC- dysfunction subscale at 3-4 weeks; Group 1: mean 16.79 (SD 9.18); n=14, Group 2: mean 26.93 (SD 9.06); n=14; WOMAC-dysfunction subscale 0-1700 Top=High is poor outcome; Comments: Baseline values: acupressure group: 36.07(10.55), sham (placebo) group: 36.43(9.44) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline values for WOMAC pain subscale: acupressure group: 9.14 (2.31), sham (placebo) group: 9.86 (2.71) usual care group: 2.78 (2.78); Group 1 Number missing: 1, Reason: discontinued intervention due to lack of interest.; Group 2 Number missing: 1, Reason: discontinued intervention due to being discharged. Protocol outcome 2: Pain at </=3 months - Actual outcome: WOMAC- pain subscale at 3-4 weeks; Group 1: mean 2.71 (SD 1.27); n=14, Group 2: mean 7.64 (SD 3.52); n=14; WOMAC- pain subscale 0-500 Top=High is poor outcome; Comments: Baseline values: acupressure group: 9.14 (2.31),sham (placebo) group: 9.86(2.71) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline values for WOMAC pain subscale: acupressure group: 9.14 (2.31), sham (placebo) group: 9.86 (2.71) usual care group: 2.78 (2.78); Group 1 Number missing: 1, Reason: discontinued intervention due to lack of interest.; Group 2 Number missing: 1, Reason: discontinued intervention due to being discharged. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY versus NO TREATMENT Protocol outcome 1: Physical function at </=3 months - Actual outcome: WOMAC- dysfunction subscale at 3-4 weeks; Group 1: mean 16.79 (SD 9.18); n=14, Group 2: mean 32.48 (SD 10.07); n=21; WOMAC-dysfunction subscale 0-1700 Top=High is poor outcome; Comments: Baseline values: acupressure group: 36.07 (10.55), usual care group: 32.00(10.06) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline values for WOMAC pain subscale: acupressure group: 9.14 (2.31), sham (placebo) group: 9.86 (2.71) usual care group: 2.78 (2.78); Blinding details: Study was single blind but this would not be possible for this comparison.; Group 1 Number missing: 1, Reason: discontinued intervention due to lack of interest.; Group 2 Number missing: 0 Protocol outcome 2: Pain at </=3 months - Actual outcome: WOMAC- pain subscale at 3-4 weeks; Group 1: mean 2.71 (SD 1.27); n=14, Group 2: mean 9.05 (SD 2.75); n=21; WOMAC- pain subscale 0-500 Top=High is poor outcome; Comments: Baseline values: acupressure group: 9.14 (2.31), usual care group: 2.78 (2.78) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline values for WOMAC pain subscale: acupressure group: 9.14 (2.31), sham (placebo) group: 9.86 (2.71) usual care group: 2.78 (2.78); Blinding details: Study was single blind but this would not be possible for this comparison.; Group 1 Number missing: 1, Reason: discontinued intervention due to lack of interest.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health related quality of life at </=3 months; Health related quality of life at > 3 months; Physical function at > 3 months; Pain at > 3 months; Psychological distress at </=3 months; Psychological distress at > 3 months; Osteoarthritis flares at </=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at </=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at </=3 months; Moderate/major adverse events at > 3 months

Study	Altinbilek 2018[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Turkey; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosed as bilateral primary knee OA according to the American College of Rheumatology criteria. The anteroposterior and lateral knee radiographs taken to stage OA according to the Kellgren and Lawrence radiological staging scale.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Stages II-III on the Kellgren and Lawrence radiological staging scale
Exclusion criteria	Inflammatory arthritis, soft tissue rheumatism an inflammation in the knee joint, higher erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), history of knee surgery, trauma (meniscopathy or instability), intraarticular intervention or physical therapy within the last six months. Also, patients using anti-inflammatory drugs other than simple analgesics, those using knee braces, patients with vascular and cardiovascular disease, paresis or neuropathy, intraarticular neoplasm, osteonecrosis and mental mood disorder and those with knee contracture.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 54.8 (8.5). Gender (M:F): 9:76. Ethnicity: Not stated.
Further population details	1. Age: ≤ 75 years 2. Diagnosis with or without imaging: Diagnosis with imaging 3. Multimorbidity: High morbidity (Presence of multi-morbidities: 25 (56.8%) versus 29 (70.7%)). 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Severity: Kellgren 2: 33 (75%) versus 33 (80.5%); Kellgren 3: 11 (25%) versus 8 (19.5%). Duration of symptoms: median 2 (0.25 to 15) versus 2 (0.25 to 15).
Indirectness of population	No indirectness

Interventions	(n=50) Intervention 1: Manual therapy and exercise combined - Manipulation and/or mobilisation and exercise. 3 minutes mobilisation, 3 minutes compression for bilateral patellofemoral and tibiofemoral joint respectively with one minute intervals in addition to the exercise program. The exercise program included: quadriceps isometric strengthening straight leg lifting, iliotibial band, hamstring stretching, strengthening abductor and adductor muscle of the hip and stretching exercises was applied as 10-repetitive 3 set, two days a week, totally four sessions, in the clinic, and the program was taught to the patients for applying two times a day at home. . Duration 3 minutes mobilisation, 3 minutes compression. Exercise was 10 repetitive 3 sets 2 days per week, total of four sessions. . Concurrent medication/care: Patients were not allowed to take NSAIDs one week before beginning of study and during the study period. They were allowed to take paracetamol up to 3g daily for pain control. Drugs they used for systemic diseases continued. . Indirectness: No indirectness Further details: 1. Type of manual intervention: Mobilisation/manipulation (n=50) Intervention 2: Exercise - Exercise (compared to manual therapy and exercise only). The exercise program included: quadriceps isometric strengthening straight leg lifting, iliotibial band, hamstring stretching, strengthening abductor and adductor muscle of the hip and stretching exercises was applied as 10-repetitive 3 set, two days a week, totally four sessions, in the clinic, and the program was taught to the patients for applying two times a day at home. . Duration 10 repetitive 3 set 2 days per week, total of four sessions.. Concurrent medication/care: Patients were not allowed to take NSAIDs one week before beginning of study and during the study period. They were allowed to take paracetamol up to 3g daily for pain control. Drugs they used for systemic diseases continued.. Indirectness: No indirectness Further details: 1. Type of manual intervention:
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANIPULATION AND/OR MOBILISATION AND EXERCISE versus EXERCISE (COMPARED TO MANUAL THERAPY AND EXERCISE ONLY)

Protocol outcome 1: Physical function at ≤/=3 months
- Actual outcome: WOMAC physical at 4 weeks; Group 1: mean 29.3 (SD 10.3); n=44, Group 2: mean 43.2 (SD 15.2); n=41; WOMAC physical function score 0-85 Top=High is poor outcome; Comments: Baseline manual therapy: 46.9 (10.3). Baseline exercise: 47.6 (12.9).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: Left of their own free will ; Group 2 Number missing: 9, Reason: Left of their own free will

Protocol outcome 2: Pain at ≤/=3 months - Actual outcome: WOMAC pain at 4 weeks ; Group 1: mean 7.8 (SD 2.8); n=44, Group 2: mean 12.3 (SD 4.5); n=41; WOMAC pain score 0-25 Top=High is poor outcome; Comments: Baseline manual therapy: 13.7 (3.4). Baseline exercise: 14.3 (4.2). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: Left of their own free will ; Group 2 Number missing: 9, Reason: Left of their own free will	
Protocol outcomes not reported by the study	Health related quality of life at ≤/=3 months; Health related quality of life at > 3 months; Physical function at > 3 months; Pain at > 3 months; Psychological distress at ≤/=3 months; Psychological distress at > 3 months; Osteoarthritis flares at ≤/=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at ≤/=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at ≤/=3 months; Moderate/major adverse events at > 3 months

Study	Cheung 2020[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=35)
Countries and setting	Conducted in Hong Kong (China); Setting: Community
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A diagnosis of knee OA based on fulfillment of any 3 of the clinical criteria developed by Altman et al (morning stiffness≤ 30 min, crepitus on active joint motion, bone tenderness, bone enlargement and no palpable joint warmth).
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Self-rated knee pain ≥3 and ≤7 on an 11 point numeric rating scale lasting for at least 3 months.(2) A diagnosis of knee OA based on fulfilment of any 3 of the clinical criteria developed by Altman et al (morning stiffness≤ 30 min, crepitus on active joint motion, bone tenderness, bone enlargement and no palpable joint warmth).(3) Chinese ethnicity (4) Age 50-70 years (5) Able to provide informed consent. (6) Ability to comprehend Chinese.
Exclusion criteria	(1)Medical diagnoses or conditions that would preclude individuals from active participation (e.g. bleeding disorders, alcohol or drug abuse. (2) Cognitive impairment preventing informed consent or understanding of the instructions (score <22 in the Hong Kong Montreal Cognitive Assessment). (3) Participation in other interventional KOA research studies. (4)Skin lesions or infections at the planned treatment sites. (5) Obesity (defined as BMI>25) (6) knee pain related to other conditions (e.g. cancer, fracture, RA or rheumatism) (7) previous foot injury or trauma (8) use of steroids for knee pain (8) pregnancy or contemplation of pregnancy (10) receipt of self-administered acupressure in the past 6 months.
Recruitment/selection of patients	Community living participants were recruited through advertisements at the university clinic of the Hong Kong Polytechnic University and social network media such as Facebook and WhatsApp.
Age, gender and ethnicity	Age - Mean (SD): 62.14 (5.93). Gender (M:F): 27F/8M. Ethnicity: Chinese ethnicity
Further population details	1. Age: < 75 years (Age 50-70 years). 2. Diagnosis with or without imaging: Diagnosis without imaging (A diagnosis of knee OA based on fulfilment of any 3 of the clinical criteria developed by Altman et al (morning stiffness≤ 30 min, crepitus on active joint

	motion, bone tenderness, bone enlargement and no palpable joint warmth). 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Duration of knee pain (months): acupressure group: 51.35 (46.91), education group: 51.53 (79.21) Severity (pain intensity): acupressure group: 9.06 (0.71), education group: 9.00 (0.69)
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Manual therapy alone - Acupressure/trigger point therapy. participants in the acupressure group received two weekly 90 minute self-administered acupressure training sessions (groups of 4-6) delivered by a registered Chinese Medicine practitioner with at least 5 years of clinical experience in acupuncture and acupressure. the acupressure protocol, using the acronym WARM (Warm-up, Acupressure, Rubbing the knee cap and Moving the knee) was based on traditional Chinese medicine meridian theory with reference to the literature and was modified by the investigators with expertise in acupuncture. It included a total of 8 acupressure points. To ensure consistency, participants were asked to demonstrate the acupressure technique at the end of training and were assessed by the practitioner. Participants were told to perform acupressure for 15-20 minutes on their painful knee (s) twice a day: once in the morning (within 1 hour of waking) and once at night (within 1 hour of dinner) for 6 weeks. each participant received a written self-administered acupressure protocol and a logbook in which to record their daily acupressure practice at home.. Duration 6 weeks. Concurrent medication/care: Participants in both groups received follow-up phone calls twice per week for 6 weeks to remind them of the self-practice/ self-care and to ask about any adverse events. Participants were advised to maintain their routine medical care for KOA, including medications and physician visits. Any changes in the use of pain medication during the intervention and evaluation periods were recorded. . Indirectness: No indirectness Further details: 1. Type of manual intervention: Soft tissue techniques (Acupressure). (n=18) Intervention 2: No manual therapy - No treatment. Participants in this group attended two weekly 90 minute health education sessions related to KOA management delivered by a registered nurse. A total of six self-care strategies were recommended, including minimization of weight bearing on the knee joint and avoidance of prolonged standing or walking. A written summary of the health education content and a progress log for recording the use of self-care strategies were distributed.. Duration 6 weeks. Concurrent medication/care: Participants in both groups received follow-up phone calls twice per week for 6 weeks to remind them of the self-practice/ self-care and to ask about any adverse events. Participants were

	advised to maintain their routine medical care for KOA, including medications and physician visits. Any changes in the use of pain medication during the intervention and evaluation periods were recorded. . Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY versus KNEE HEALTH EDUCATION

Protocol outcome 1: Health related quality of life at </=3 months
- Actual outcome: SF-6D at 6 weeks; Group 1: mean 0.672 (SD 0.029); n=17, Group 2: mean 0.744 (SD 0.028); n=18; SF-6D 6-31? Top=High is poor outcome; Comments: Data reported is mean plus SEM, not SD
Baseline values: acupressure group: 0.668 (0.029), education group: 0.695(0.028)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: dropped out of study; Group 2 Number missing: 0

Protocol outcome 2: Physical function at </=3 months
- Actual outcome: WOMAC- function subscale at 6 weeks; Group 1: mean 20.59 (SD 2.71); n=17, Group 2: mean 21.44 (SD 2.56); n=18; WOMAC- function subscale 0-68 Top=High is poor outcome; Comments: Values reported are mean plus SEM, not SD
Baseline values: acupressure group: 28.29 (2.64), education group: 27.67 (2.56)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: dropped out of study; Group 2 Number missing: 0

Protocol outcome 3: Pain at </=3 months
- Actual outcome: WOMAC- pain subscale at 6 weeks; Group 1: mean 6.98 (SD 0.74); n=17, Group 2: mean 6.44 (SD 0.69); n=18; WOMAC- pain subscale 0-20 Top=High is poor outcome; Comments: Values reported are mean plus SEM, not SD
Baseline values: acupressure group: 9.06 (0.71), education group: 9.00 (0.69)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: dropped out of study; Group 2 Number missing: 0

Protocol outcome 4: Minor adverse events at </=3 months
- Actual outcome: Adverse events- pain at stimulation site, worsening of knee pain, pricking pain sensation on legs, bruising at stimulation sites at 6 weeks; Group 1: 7/17, Group 2: 0/18
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: dropped out of study; Group 2 Number

missing: 0	
Protocol outcomes not reported by the study	Health related quality of life at > 3 months; Physical function at > 3 months; Pain at > 3 months; Psychological distress at </=3 months; Psychological distress at > 3 months; Osteoarthritis flares at </=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at > 3 months; Moderate/major adverse events at </=3 months; Moderate/major adverse events at > 3 months

Study	Choi 2019[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in South Korea; Setting: Hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients had been diagnosed by their attending doctors with knee degenerative arthritis based on clinical findings and X-ray images.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age over 60 years, K/L grade>2, and not currently exercising.
Exclusion criteria	Receiving drug treatment, ligament damage, infection, CNS disorder or cognitive disorder.
Recruitment/selection of patients	Participants were selected from patients who had either been hospitalised at Sunhan hospital or who had visited the hospital as outpatients.
Age, gender and ethnicity	Age - Mean (SD): Knee joint traction group: 67.53 (4.13); Control group: 65.40 (4.88). Gender (M:F): 15M/ 15F. Ethnicity: Not reported
Further population details	1. Age: Systematic review: mixed (Age >60 years). 2. Diagnosis with or without imaging: Diagnosis with imaging (X-ray imaging used as part of diagnosis.). 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Symptom duration (not stated whether this is months): Knee joint traction group: 12.06 (2.01); Control group: 13.06 (2.21) Symptom severity (K-L grade, %): Knee joint traction group: 2.26(0.45); Control group: 2.66(0.61)
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Manual therapy alone - Manipulation and/or mobilisation. the experimental group received a knee joint traction workout for 20 minutes a day, five times a week. The participants were asked to bend their hip and knee joints at 60 degrees in the supine position. The tibia and thigh were secured with a strap and continuous knee joint traction treatment was applied to tow the tibia in the cephalocaudal direction. The force that was applied by the traction was approximately equal to 6% of the participant's weight., and the traction continued for a 20 minute

	stretch.. Duration 4 weeks. Concurrent medication/care: Both groups received general physical therapy, which was carried out in three ways and included 20 minutes of superficial heat therapy, 5 minutes of deep heat therapy and 20 minutes of electric therapy five times a week.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Mobilisation/manipulation (knee joint traction). (n=15) Intervention 2: No manual therapy - No treatment. Both groups received general physical therapy, which was carried out in three ways and included 20 minutes of superficial heat therapy, 5 minutes of deep heat therapy and 20 minutes of electric therapy five times a week.. Duration 4 weeks. Concurrent medication/care: None reported. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANIPULATION AND/OR MOBILISATION (KNEE JOINT TRACTION) versus GENERAL PHYSICAL THERAPY

Protocol outcome 1: Physical function at </=3 months
- Actual outcome: WOMAC score- physical function at 4 weeks; Group 1: mean -21.86 (SD 3.29); n=15, Group 2: mean -8.86 (SD 3.77); n=15; WOMAC-physical function 0-61 Top=High is poor outcome; Comments: States that it is measuring physical function but description is of total WOMAC score (24 categories).
Baseline values: intervention group: 47.20 (1.65), control group: 44.13 (2.29)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline VAS score: intervention: 7.13 (0.91), control: 6.06 (0.88) Baseline BDI score: intervention: 22.33 (1.34), control: 19.53 (1.18); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain at </=3 months
- Actual outcome: VAS score at 4 weeks; Group 1: mean -4.73 (SD 0.96); n=15, Group 2: mean -1 (SD 1.06); n=15; VAS 0-10 Top=High is poor outcome; Comments: Baseline VAS score: knee traction group (mean plus SD): 7.13 (0.91), control group: 6.06 (0.88)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline VAS score: intervention: 7.13 (0.91), control: 6.06 (0.88) Baseline BDI score: intervention: 22.33 (1.34), control: 19.53 (1.18); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Psychological distress at </=3 months
- Actual outcome: BDI score at 4 weeks; Group 1: mean -8.53 (SD 1.72); n=15, Group 2: mean -1.4 (SD 1.76); n=15; Beck depression inventory 0-63 Top=High is poor outcome; Comments: Baseline values: intervention group: 22.33(1.34), control group: 19.53 (1.18)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline VAS score: intervention: 7.13 (0.91), control: 6.06 (0.88) Baseline BDI score: intervention: 22.33 (1.34), control: 19.53 (1.18); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health related quality of life at </=3 months; Health related quality of life at > 3 months; Physical function at > 3 months; Pain at > 3 months; Psychological distress at > 3 months; Osteoarthritis flares at </=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at </=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at </=3 months; Moderate/major adverse events at > 3 months

Study	Fitzgerald 2016[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in USA; Setting: Three sites in the USA: Departments of Physical Therapy at the University of Pittsburgh, Pittsburgh PA, Intermountain Healthcare, Salt Lake City, Utah and the San Antonio Military Medical Centre, San Antonio, TX.
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Meet American College of Rheumatology's 1986 Clinical Criteria for KOA.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>/=40 years of age; meet American College of Rheumatology's 1986 Clinical Criteria for KOA.
Exclusion criteria	If did not meet the ACR criteria; scheduled for total knee arthroplasty (TKA); had undergone total joint arthroplasty of any lower extremity joint; exhibited uncontrolled hypertension; currently have back or leg pain in other areas beside knee that affects ability to perform physical activities; history of neurological disorders that would affect lower extremity function (stroke, peripheral neuropathy, Parkinson's disease, multiple sclerosis).
Recruitment/selection of patients	Referred from physician offices; individuals registered in the authors' institutional research participant registries were informed of the studies by the registries and contacted them directly; and individuals received notification of the study through public announcements via paper flyers, radio, and hospital television monitors at participating sites and contacted them directly.
Age, gender and ethnicity	Age - Mean (SD): Exercise group: 58.3 (10); MT + Exercise group: 58 (9.8). Gender (M:F): 101:199. Ethnicity: Not stated.
Further population details	1. Age: ≤ 75 years 2. Diagnosis with or without imaging: Diagnosis without imaging 3. Multimorbidity: Not applicable 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Exercise group vs MT + exercise group: Knee pain rating scale: 5.4 (2.4); 5.7 (2.3). Duration of knee symptoms: ≤1 year 8 (10.7%); 9 (12%) 1-2 years 12 (16%); 7 (9.3%)

	3-5 years 14 (18.7%); 13 (17.3%) 5-10 years 25 (33.3%); 27 (36%) > 10 years 16 (21.3%); 19 (25.3%).
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Manual therapy and exercise combined - Combined active and passive manual therapy and exercise. Manoeuvres applied with manual force from the treating therapist, with techniques based on those recommended for reducing pain and improving function in people with KOA> Core MT techniques included those specifically addressing knee joint mobility/flexibility and soft tissue manipulations of the quadriceps, rectus femoris, hamstring and gastrocenemius muscles and peripatellar tissues. Additional but optional manual techniques were provided for hip, foot and ankle joints if indicated by deficits on initial examination. The exercise therapy was a 10 minute aerobic (treadmill walk or stationary cycling) warm-up; then a series of strengthening, stretching, and neuromuscular control (agility and balance training techniques), considered core exercises. The therapists had the option to select additional exercise activities, based on initial examination findings, which addressed strength or flexibility in the hip and ankle if impairments were identified on initial examination. . Duration 9 weeks. The exercise therapy session averaged 45 minutes to an hour. The MT added an additional 15-20 minutes per session. . Concurrent medication/care: All participants received 12 supervised therapy sessions. . Indirectness: No indirectness Further details: 1. Type of manual intervention: Mixed (n=75) Intervention 2: Exercise - Exercise (compared to manual therapy and exercise only). The exercise therapy was a 10 minute aerobic (treadmill walk or stationary cycling) warm-up; then a series of strengthening, stretching, and neuromuscular control (agility and balance training techniques), considered core exercises. The therapists had the option to select additional exercise activities, based on initial examination findings, which addressed strength or flexibility in the hip and ankle if impairments were identified on initial examination. . Duration 9 weeks. The exercise therapy session averaged 45 minutes to an hour. . Concurrent medication/care: All participants received 12 supervised therapy sessions. . Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	Academic or government funding (Grant from the Agency for Healthcare Research and Quality (AHRQ), grant# R01HS019624-01.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINED ACTIVE AND PASSIVE MANUAL THERAPY AND EXERCISE versus EXERCISE (COMPARED TO MANUAL THERAPY AND EXERCISE ONLY) Protocol outcome 1: Pain at ≤/=3 months - Actual outcome: Knee pain rating at 9 weeks; Group 1: mean -1.6 (SD 0.7); n=75, Group 2: mean -2.2 (SD 0.3); n=75; Knee pain rating 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Knee pain rating scale 59.6 (35.6) in MT + exercise group; 5.4 (2.4) in exercise group; Blinding details: The exercise component in either arm could be different exercises specific to the participant's requirements. ; Group 1 Number missing: 3, Reason: Lost to follow-up; Group 2 Number missing: 3, Reason: Lost to follow-up Protocol outcome 2: Pain at > 3 months - Actual outcome: Knee pain rating at 1 year; Group 1: mean -0.9 (SD 0.7); n=75, Group 2: mean -1.3 (SD 0.3); n=75; Knee pain rating 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Knee pain rating scale 59.6 (35.6) in MT + exercise group; 5.4 (2.4) in exercise group; Blinding details: The exercise component in either arm could be different exercises specific to the participant's requirements. ; Group 1 Number missing: 3, Reason: Lost to follow-up; Group 2 Number missing: 7, Reason: Lost to follow-up	
Protocol outcomes not reported by the study	Health related quality of life at ≤/=3 months; Health related quality of life at > 3 months; Physical function at ≤/=3 months; Physical function at > 3 months; Psychological distress at ≤/=3 months; Psychological distress at > 3 months; Osteoarthritis flares at ≤/=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at ≤/=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at ≤/=3 months; Moderate/major adverse events at > 3 months

Study	Guo 2021[55]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=221)
Countries and setting	Conducted in China; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee osteoarthritis by the American College of Rheumatology clinical criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 18 years old; diagnosed with knee osteoarthritis by American College of Rheumatology clinical criteria; knee pain for at least 3 months (visual analogue scale score at least 4).
Exclusion criteria	Serious medical conditions; knee replacement; corticosteroids or hyaluronate usage; knee arthroscopy or injury in the past year; regular use of massage therapy.
Recruitment/selection of patients	No additional information.
Age, gender and ethnicity	Age - Mean (SD): 62.7 (7.9). Gender (M:F): 97:105. Ethnicity: Not stated/unclear
Further population details	1. Age: < 75 years 2. Diagnosis with or without imaging: Not stated / Unclear 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Severity: Not stated/unclear Duration of symptoms (mean [SD]): 5.9 (5.4) years
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Manual therapy and exercise combined - Acupressure/trigger point therapy and exercise. Exercise and acupressure (for 16 weeks). In the first 8 weeks, people were taught to complete all treatments at home, in the next 8-16 weeks they conducted telephone follow-ups to understand and supervised self-management. The participants were asked to follow the intervention and make a report every day. Exercise consisted of warm-up exercises, aerobic exercises for the legs, muscle strengthening and nerve response. These exercises were taught in eight weeks of lectures. Exercises were to be completed three times a week at home. The acupressure group were asked to perform a series of acupressure points on their own. These points included SP9 and 10 (Yinlingquan and Xuehai), ST 34, 35 and 36 (Liangqiu, Dubi and Zusanli), EX-LE 2 and 4 (Heding and Neixiyan) and GB 34

	(Yanglingquan). People were asked to massage these acupoints one by one, each for 5 minutes. Participants were asked to do this treatment 3 times a day, 5 days a week. People with restricted movement were asked to ask a helper to perform the same acupressure.. Duration 16 weeks. Concurrent medication/care: All people received basic care designed by their clinicians or family doctors.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Soft tissue techniques (n=55) Intervention 2: Manual therapy alone - Acupressure/trigger point therapy. Acupressure regimen only. Duration 16 weeks. Concurrent medication/care: All people received basic care designed by their clinicians or family doctors.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Soft tissue techniques (n=56) Intervention 3: Exercise - Exercise (compared to manual therapy and exercise only). Exercise regimen only. Duration 16 weeks. Concurrent medication/care: All people received basic care designed by their clinicians or family doctors.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable (n=55) Intervention 4: No manual therapy - No treatment. No manual therapy. Duration 16 weeks. Concurrent medication/care: All people received basic care designed by their clinicians or family doctors.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY AND EXERCISE versus ACUPRESSURE/TRIGGER POINT THERAPY

Protocol outcome 1: Physical function at </=3 months
- Actual outcome: WOMAC function at 8 weeks; Group 1: mean 20.2 (SD 10.9); n=51, Group 2: mean 24.2 (SD 9.6); n=49; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 31.7 (7.9). Baseline acupressure: 32.5 (7.2).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 3, Reason: 1 lost interest, 2 time constraints; Group 2 Number missing: 4, Reason: 3 lost interest, 1 other health condition

Protocol outcome 2: Physical function at > 3 months

- Actual outcome: WOMAC function at 16 weeks; Group 1: mean 18.5 (SD 11.6); n=51, Group 2: mean 21.1 (SD 10.8); n=49; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 31.7 (7.9). Baseline acupressure: 32.5 (7.2).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 4, Reason: 1 lost interest, 2 time constraints, 1 declined to participate; Group 2 Number missing: 6, Reason: 3 lost interest, 1 other health condition, 2 declined to participate

Protocol outcome 3: Pain at </=3 months
- Actual outcome: WOMAC pain at 8 weeks; Group 1: mean 5.7 (SD 3.2); n=51, Group 2: mean 7.3 (SD 2.8); n=49; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 8.8 (2.6). Baseline acupressure: 9.0 (2.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 3, Reason: 1 lost interest, 2 time constraints; Group 2 Number missing: 4, Reason: 3 lost interest, 1 other health condition

Protocol outcome 4: Pain at > 3 months
- Actual outcome: WOMAC pain at 16 weeks; Group 1: mean 4.8 (SD 2.7); n=51, Group 2: mean 6.5 (SD 3); n=49; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 8.8 (2.6). Baseline acupressure: 9.0 (2.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 4, Reason: 1 lost interest, 2 time constraints, 1 declined to participate; Group 2 Number missing: 6, Reason: 3 lost interest, 1 other health condition, 2 declined to participate

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY AND EXERCISE versus EXERCISE (COMPARED TO MANUAL THERAPY AND EXERCISE ONLY)

Protocol outcome 1: Physical function at </=3 months
- Actual outcome: WOMAC function at 8 weeks; Group 1: mean 20.2 (SD 10.9); n=51, Group 2: mean 23.4 (SD 10.8); n=50; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 31.7 (7.9). Baseline exercise: 30.7 (7.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 3, Reason: 1 lost interest, 2 time constraints; Group 2 Number missing: 5, Reason: 3 declined to participate, 2 time constraints

Protocol outcome 2: Physical function at > 3 months
- Actual outcome: WOMAC function at 16 weeks; Group 1: mean 18.5 (SD 11.6); n=51, Group 2: mean 19.8 (SD 11.3); n=50; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 31.7 (7.9). Baseline exercise: 30.7 (7.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 4, Reason: 1 lost interest, 2 time constraints, 1 declined to participate; Group 2 Number missing: 6, Reason: 3 declined to participate, 2 time constraints, 1 declined to participate

Protocol outcome 3: Pain at </=3 months
- Actual outcome: WOMAC pain at 8 weeks; Group 1: mean 5.7 (SD 3.2); n=51, Group 2: mean 7.1 (SD 3); n=56; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 8.8 (2.6). Baseline exercise: 8.7 (2.6).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 3, Reason: 1 lost interest, 2 time constraints; Group 2 Number missing: 5, Reason: 3 declined to participate, 2 time constraints

Protocol outcome 4: Pain at > 3 months
- Actual outcome: WOMAC pain at 16 weeks; Group 1: mean 4.8 (SD 2.7); n=51, Group 2: mean 5.9 (SD 2.5); n=56; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 8.8 (2.6). Baseline exercise: 8.7 (2.6).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 4, Reason: 1 lost interest, 2 time constraints, 1 declined to participate; Group 2 Number missing: 6, Reason: 3 declined to participate, 2 time constraints, 1 declined to participate

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY AND EXERCISE versus NO TREATMENT

Protocol outcome 1: Physical function at </=3 months
- Actual outcome: WOMAC function at 8 weeks; Group 1: mean 20.2 (SD 10.9); n=51, Group 2: mean 27.9 (SD 10); n=52; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 31.7 (7.9). Baseline no treatment: 31.2 (7.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 3, Reason: 1 lost interest, 2 time constraints; Group 2 Number missing: 2, Reason: 2 declined to participate

Protocol outcome 2: Physical function at > 3 months
- Actual outcome: WOMAC function at 16 weeks; Group 1: mean 18.5 (SD 11.6); n=51, Group 2: mean 25.7 (SD 10.9); n=52; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 31.7 (7.9). Baseline no treatment: 31.2 (7.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 4, Reason: 1 lost interest, 2 time constraints, 1 declined to participate; Group 2 Number missing: 6, Reason: 3 declined to participate, 2 time constraints, 1 declined to participate

Protocol outcome 3: Pain at </=3 months
- Actual outcome: WOMAC pain at 8 weeks; Group 1: mean 5.7 (SD 3.2); n=51, Group 2: mean 8.1 (SD 2.9); n=52; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 8.8 (2.6). Baseline no treatment: 8.8 (2.4).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 3, Reason: 1 lost interest, 2 time constraints; Group 2 Number missing: 2, Reason: 2 declined to participate

Protocol outcome 4: Pain at > 3 months
- Actual outcome: WOMAC pain at 16 weeks; Group 1: mean 4.8 (SD 2.7); n=51, Group 2: mean 7.6 (SD 2.8); n=52; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure and exercise: 8.8 (2.6). Baseline no treatment: 8.8 (2.4).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 4, Reason: 1 lost interest, 2 time constraints, 1 declined to participate; Group 2 Number missing: 3, Reason: 2 declined to participate, 1 declined to participate

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY versus NO TREATMENT

Protocol outcome 1: Physical function at </=3 months
- Actual outcome: WOMAC function at 8 weeks; Group 1: mean 24.2 (SD 9.6); n=49, Group 2: mean 27.9 (SD 10); n=52; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure: 32.5 (7.2). Baseline no treatment: 31.2 (7.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 4, Reason: 3 lost interest, 1 other health conditions; Group 2 Number missing: 2, Reason: 2 declined to participate

Protocol outcome 2: Physical function at > 3 months
- Actual outcome: WOMAC function at 16 weeks; Group 1: mean 21.1 (SD 10.8); n=49, Group 2: mean 25.7 (SD 10.9); n=52; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure: 32.5 (7.2). Baseline no treatment: 31.2 (7.7).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 6, Reason: 3 lost interest, 1 other health conditions, 2 declined to participate; Group 2 Number missing: 3, Reason: 3 declined to participate

Protocol outcome 3: Pain at </=3 months
- Actual outcome: WOMAC pain at 8 weeks; Group 1: mean 7.3 (SD 2.8); n=49, Group 2: mean 8.1 (SD 2.9); n=52; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure: 9.0 (2.7). Baseline no treatment: 8.8 (2.4).

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 4, Reason: 3 lost interest, 1 other health conditions; Group 2 Number missing: 2, Reason: 2 declined to participate Protocol outcome 4: Pain at > 3 months - Actual outcome: WOMAC pain at 16 weeks; Group 1: mean 6.5 (SD 3); n=49, Group 2: mean 7.6 (SD 2.8); n=52; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure: 9.0 (2.7). Baseline no treatment: 8.8 (2.4). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, weight, female, BMI, education level, employment status, marital status, symptom duration and baseline values of outcomes; Group 1 Number missing: 6, Reason: 3 lost interest, 1 other health conditions, 2 declined to participate; Group 2 Number missing: 3, Reason: 3 declined to participate	
Protocol outcomes not reported by the study	Health related quality of life at </=3 months; Health related quality of life at > 3 months; Psychological distress at </=3 months; Psychological distress at > 3 months; Osteoarthritis flares at </=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at </=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at </=3 months; Moderate/major adverse events at > 3 months

Study	Nigam 2021[77]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in India; Setting: General hospital physiotherapy clinic.
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis made by orthopaedic surgeon based on ACR clinical criteria.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Score between 1 and 3 on the K-L scale, age 50-70 years, knee pain of duration greater than 3 months and intensity between 4 and 8 on a 10 cm VAS at the time of presentation. They were required to be able to stand up independently from a chair and to be able to lay prone.
Exclusion criteria	Recent lower limb fractures, any neurological condition contraindicated to manual therapy, past traumatic knee osteoarthritis, total knee arthroplasty, uncontrolled hypertension, radiating leg pain and BMI >30.
Recruitment/selection of patients	Consecutive patients presenting to the physiotherapy outpatient department were recruited.
Age, gender and ethnicity	Age - Mean (SD): MWM group: 58.5 (4.36), control group: 59.4 (6.57). Gender (M:F): 15M/25F. Ethnicity: Not reported
Further population details	1. Age: < 75 years (age 50-70 years). 2. Diagnosis with or without imaging: Diagnosis without imaging (ACR clinical criteria.). 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Severity: MWM group: 6.4 (1.4), control group: 6.3 (1.3) Duration of symptoms (months [SD]): MWM group: 9.6 (9.73), control group: 9.8 (9.34)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Manual therapy and exercise combined - Manipulation and/or mobilisation and exercise. Mobilisation with movement plus exercise and moist heat. Interventions were provided individually by a physiotherapist with formal training in mobilisation with movement. To begin, all participants received moist heat for 15 minutes from a hydrocollator pack wrapped in soft towel applied around the affected knee. Following this, an exercise programme was initiated. This programme was

	designed to improve muscle strength of the hip, knee and ankle musculature. Exercises included pelvic bridging, resisted knee flexion and extension, mini squats and heel raises. Pelvic bridging was performed against body weight resistance in crook lying, lifting up the pelvis for five seconds. Knee flexion was performed in prone lying while knee extension was performed in sitting. Resistance was provided with a weighted ankle cuff commencing at 1kg and progressing to 2kg depending on the patient's comfort. mini squat exercises were undertaken in standing and involved closed chain hip and knee flexion as far as comfort allowed. Single leg heel raise exercise was performed in standing against body weight resistance. Exercises were progressed from 15 repetitions x 3 sets to 20 repetitions x 5 sets as per the capability of the participant. All exercises were supervised during the sessions and exercise parameters were adjusted if required but without any modifications in the type of exercise. Recommendations were made for the participants to undertake similar exercise at home, however adherence was not formally checked. All participants were advised to undertake brisk walking daily for 20 minutes. In addition to exercise and moist heat, participants in the intervention group received mobilisation with movement. This was applied to the affected knee prior to the exercise programme. With the patient lying supine, the therapist applied a pain-free manual sustained glide force to the proximal tibia close tot he knee joint (with counterforce on the femur) either in a lateral, medial, rotational, anterior or posterior direction. While this force was maintained, the participant was instructed to move their affected knee in the symptomatic direction, being either towards flexion or extension as far as possible without pain. The direction of the glide which had the most beneficial effect on improving pain-free range of motion was chosen for the treatment. If the participant was able to achieve end range without pain, pain-free overpressure was applied by the therapist. The technique was progressed to weight-bearing once fill range was achieved without pain in lying. Three sets of 6 to 10 repetitions of the successful mobilisation with movement were delivered in each session. A self-applied mobilisation with movement, mimicking the therapist technique, was taught to the participants in the first treatment session. Participants were advised to perform self-mobilisation with movement only if improvements in pain free range was achieved during its application. Participants were allowed to alter the dose of self- applied mobilisation with movement based on their pain pattern during daily activities. In cases of bilateral symptoms, the limb with the greatest pain was considered the affected limb to be treated. All participants attended the clinic for six 45 minute treatment sessions carried out over two consecutive weeks. . Duration 2 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness

	Further details: 1. Type of manual intervention: Mobilisation/manipulation (Mobilisation with movement). (n=20) Intervention 2: Exercise - Exercise (compared to manual therapy and exercise only). Interventions were provided individually by a physiotherapist with formal training in mobilisation with movement. To begin, all participants received moist heat for 15 minutes from a hydrocollator pack wrapped in soft towel applied around the affected knee. Following this, an exercise programme was initiated. This programme was designed to improve muscle strength of the hip, knee and ankle musculature. Exercises included pelvic bridging, resisted knee flexion and extension, mini squats and heel raises. Pelvic bridging was performed against body weight resistance in crook lying, lifting up the pelvis for five seconds. Knee flexion was performed in prone lying while knee extension was performed in sitting. Resistance was provided with a weighted ankle cuff commencing at 1kg and progressing to 2kg depending on the patient's comfort. mini squat exercises were undertaken in standing and involved closed chain hip and knee flexion as far as comfort allowed. Single leg heel raise exercise was performed in standing against body weight resistance. Exercises were progressed from 15 repetitions x 3 sets to 20 repetitions x 5 sets as per the capability of the participant. All exercises were supervised during the sessions and exercise parameters were adjusted if required but without any modifications in the type of exercise. Recommendations were made for the participants to undertake similar exercise at home, however adherence was not formally checked. All participants were advised to undertake brisk walking daily for 20 minutes. All participants attended the clinic for six 45 minute treatment sessions carried out over two consecutive weeks. . Duration 2 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MOBILISATION WITH MOVEMENT AND EXERCISE versus EXERCISE (COMPARED TO MANUAL THERAPY AND EXERCISE ONLY)

Protocol outcome 1: Pain at </=3 months
- Actual outcome: 24 hour knee pain at 3 months; Group 1: mean 2.3 (SD 1); n=20, Group 2: mean 4.2 (SD 1.2); n=20; VAS 0-10 Top=High is poor outcome; Comments: Baseline values: MWM group: 6.4 (1.4), exercise group: 6.3 (1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Lost to follow-up; Group 2 Number

missing: 2, Reason: Lost to follow-up Protocol outcome 2: Pain at > 3 months - Actual outcome: 24 hour knee pain at 6 months; Group 1: mean 2 (SD 0.8); n=20, Group 2: mean 4 (SD 1.1); n=20; VAS 0-10 Top=High is poor outcome; Comments: Baseline values: MWM group: 6.4 (1.4), exercise group: 6.3 (1.3) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Lost to follow-up; Group 2 Number missing: 4, Reason: Lost to follow-up	
Protocol outcomes not reported by the study	Health related quality of life at </=3 months; Health related quality of life at > 3 months; Physical function at </=3 months; Physical function at > 3 months; Psychological distress at </=3 months; Psychological distress at > 3 months; Osteoarthritis flares at </=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at </=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at </=3 months; Moderate/major adverse events at > 3 months

Study	Pollard 2008[82]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=43)
Countries and setting	Conducted in Australia; Setting: Not reported.
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A prior medical diagnosis of OA in the knee(s) as per Forma et al (1983) and identification of the appearance of OA in one or both knees on radiographs.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Must be aged between 45 and 70 years and must suffer the following: a prior medical diagnosis of OA in the knee(s) as per Forma et al (1983); self reported mild to moderate knee pain of at least one year duration; self reported knee crepitus; self reported restricted range of motion and/or joint deformity of the knee, no history of joint replacement therapy; no recent history of meniscal or other knee surgery (less than 6 months).
Exclusion criteria	Not stated.
Recruitment/selection of patients	A print media advertising campaign.
Age, gender and ethnicity	Age - Mean (SD): 56.5 years. Gender (M:F): 29:14. Ethnicity: Not stated.
Further population details	1. Age: > 75 years 2. Diagnosis with or without imaging: Diagnosis with imaging 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Severity: 3.3 (2.6 to 4.0) versus 3.5 (2.2 to 4.7). Duration of symptoms: Chronic, non-progressive history of osteoarthritic knee pain of at least one year.
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Manual therapy alone - Manipulation and/or mobilisation. Macquarie Injury Management Group Knee Protocol: a non-invasive Myofasical Mobilisation procedure and an impulse thrust procedure performed on the symptomatic knee. In cases where OA was bilateral; mobilisation was performed on both knees. . Duration 3 treatments per week for 2 consecutive weeks. . Concurrent

	medication/care: Not stated. . Indirectness: No indirectness Further details: 1. Type of manual intervention: Mobilisation/manipulation (n=17) Intervention 2: Sham manual therapy. A palmar contact to the knee without the application of force followed by interferential set at zero. The participants were told that the procedure was a micro current application that they should not be able to feel. . Duration 3 treatments per week for 2 consecutive weeks. . Concurrent medication/care: Not stated. . Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANIPULATION AND/OR MOBILISATION versus SHAM MANUAL THERAPY Protocol outcome 1: Pain at ≤/=3 months - Actual outcome: Knee pain intensity at 2 weeks; Group 1: mean 1.9 (SD 1.69); n=26, Group 2: mean 3.1 (SD 2.1); n=17; VAS 0-11 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline values given only for pain scores, which were comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health related quality of life at ≤/=3 months; Health related quality of life at > 3 months; Physical function at ≤/=3 months; Physical function at > 3 months; Pain at > 3 months; Psychological distress at ≤/=3 months; Psychological distress at > 3 months; Osteoarthritis flares at ≤/=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at ≤/=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at ≤/=3 months; Moderate/major adverse events at > 3 months

Study	Rani 2021[86]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=240)
Countries and setting	Conducted in India; Setting: Outpatient follow up
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Knee osteoarthritis by the American College of Rheumatology clinical criteria and radiological score
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 45 years or more; unilateral knee osteoarthritis; American College of Rheumatology clinical criteria; pain intensity of 3 or more on visual analog scale (10 mm scale); able to apply pressure at acupoints precisely by self/with assistance.
Exclusion criteria	Prone to fractures that may be due to osteoporosis; suffering from acute and malignant diseases; having significant pain in any part of body whose intensity comparable to knee pain; neurological disorders like dementia, cerebral tumor, Alzheimer's disease.
Recruitment/selection of patients	Participants were recruited through advertisements in the local newspapers, community and media
Age, gender and ethnicity	Age - Mean (SD): 59.34 (6.57). Gender (M:F): 110:130. Ethnicity: Not stated/unclear
Further population details	1. Age: < 75 years 2. Diagnosis with or without imaging: Diagnosis with imaging 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Knee osteoarthritis
Extra comments	Severity: Kellgren Lawrence grade 0-4, median grade 2 Duration of symptoms (SD): 5.10 (1.34) years
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Manual therapy alone - Acupressure/trigger point therapy. Acupressure around the knee concurrently with pharmacological treatment. The acupressure treatment was delivered at six knee points, Liangqiu (ST34), Dubi (ST35), Zusanli (ST36), Yinlingquan (SP9), Xuehai (SP10), and Yang Ling Quan (GB34). The pressure was applied using a handheld device for 3 minutes, five times (15 minutes in total) taking 30s pauses. The process was repeated twice daily. People received a kit that contained a handheld device for the acupressure, a DVD, a timer, a pictorial representation of acupoints with instructions and a log book.. Duration 12

	months. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Type of manual intervention: Soft tissue techniques (n=80) Intervention 2: Sham manual therapy. Sham manual therapy and pharmacological treatment using the same device but applying pressure to points not on the meridians for knee acupressure. Same duration of treatment and this group received similar resources.. Duration 12 months. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable (n=80) Intervention 3: No manual therapy - Manual therapy plus additional treatment versus additional treatment. Pharmacological management only. Duration 12 months. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY versus SHAM MANUAL THERAPY

Protocol outcome 1: Health related quality of life at </=3 months
- Actual outcome: SF-36 physical component summary at 3 months; Group 1: mean 28.14 (SD 9.23); n=75, Group 2: mean 30.45 (SD 15.12); n=76; SF-36 physical component summary 0-100 Top=High is good outcome; Comments: Baseline acupressure: 30.12 (8.64). Baseline sham: 31.23 (7.56).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 4, Reason: 4 lost to follow up
- Actual outcome: SF-36 mental component summary at 3 months; Group 1: mean 51.34 (SD 9.45); n=75, Group 2: mean 51.24 (SD 11.89); n=76; SF-36 mental component 0-100 Top=High is good outcome; Comments: Baseline acupressure: 51.76 (9.82). Baseline sham: 50.94 (8.67).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 2: Health related quality of life at > 3 months
- Actual outcome: SF-36 physical component summary at 12 months; Group 1: mean 33.87 (SD 12.34); n=75, Group 2: mean 32.21 (SD 9.23); n=76; SF-36 physical component summary 0-100 Top=High is good outcome; Comments: Baseline acupressure: 30.12 (8.64). Baseline sham: 31.23 (7.56).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number

missing: 4, Reason: 4 lost to follow up
- Actual outcome: SF-36 mental component summary at 12 months; Group 1: mean 55.98 (SD 14.67); n=75, Group 2: mean 52.45 (SD 8.76); n=76; SF-36 mental component 0-100 Top=High is good outcome; Comments: Baseline acupressure: 51.76 (9.82). Baseline sham: 50.94 (8.67).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 3: Physical function at </=3 months
- Actual outcome: WOMAC function at 3 months; Group 1: mean 34.23 (SD 9.89); n=75, Group 2: mean 35.46 (SD 9.23); n=76; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure: 39.44 (7.71). Baseline sham: 37.15 (12.39).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 4: Physical function at > 3 months
- Actual outcome: WOMAC function at 12 months; Group 1: mean 31.2 (SD 11.54); n=75, Group 2: mean 34.67 (SD 11.21); n=76; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure: 39.44 (7.71). Baseline sham: 37.15 (12.39).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 5: Pain at </=3 months
- Actual outcome: WOMAC pain at 3 months; Group 1: mean 10.34 (SD 4.12); n=75, Group 2: mean 10.76 (SD 5.31); n=76; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure: 15.31 (8.24). Baseline sham: 13.44 (5.62).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 6: Pain at > 3 months
- Actual outcome: WOMAC pain at 12 months; Group 1: mean 8.54 (SD 3.33); n=75, Group 2: mean 11.04 (SD 4.56); n=76; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure: 15.31 (8.24). Baseline sham: 13.44 (5.62).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 4, Reason: 4 lost to follow up

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPRESSURE/TRIGGER POINT THERAPY versus MANUAL THERAPY PLUS ADDITIONAL TREATMENT VERSUS ADDITIONAL TREATMENT

Protocol outcome 1: Health related quality of life at </=3 months
- Actual outcome: SF-36 physical component summary at 3 months; Group 1: mean 28.14 (SD 9.23); n=80, Group 2: mean 27.34 (SD 9.34); n=80; SF-36 physical component summary 0-100 Top=High is good outcome; Comments: Baseline acupressure: 30.12 (8.64). Baseline no treatment: 28.99 (7.46).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 5, Reason: 5 lost to follow up
- Actual outcome: SF-36 mental component summary at 3 months; Group 1: mean 51.34 (SD 9.45); n=80, Group 2: mean 51.67 (SD 8.78); n=80; SF-36 mental component summary 0-100 Top=High is good outcome; Comments: Baseline acupressure: 51.76 (9.82). Baseline no treatment: 51.21 (8.45).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 5, Reason: 5 lost to follow up

Protocol outcome 2: Health related quality of life at > 3 months
- Actual outcome: SF-36 physical component summary at 12 months; Group 1: mean 33.87 (SD 12.34); n=75, Group 2: mean 30.85 (SD 8.67); n=75; SF-36 physical component summary 0-100 Top=High is good outcome; Comments: Baseline acupressure: 30.12 (8.64). Baseline no treatment: 28.99 (7.46).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 5, Reason: 5 lost to follow up
- Actual outcome: SF-36 mental component summary at 12 months; Group 1: mean 55.98 (SD 14.67); n=75, Group 2: mean 51.78 (SD 11.56); n=75; SF-36 mental component summary 0-100 Top=High is good outcome; Comments: Baseline acupressure: 51.76 (9.82). Baseline no treatment: 51.21 (8.45).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 5, Reason: 5 lost to follow up

Protocol outcome 3: Physical function at </=3 months
- Actual outcome: WOMAC function at 3 months; Group 1: mean 34.23 (SD 9.89); n=80, Group 2: mean 37.67 (SD 11.78); n=80; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure: 39.44 (7.71). Baseline no treatment: 39.67 (11.34).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 5, Reason: 5 lost to follow up

Protocol outcome 4: Physical function at > 3 months
- Actual outcome: WOMAC function at 12 months; Group 1: mean 31.2 (SD 11.54); n=75, Group 2: mean 37.1 (SD 15.54); n=75; WOMAC function 0-68 Top=High is poor outcome; Comments: Baseline acupressure: 39.44 (7.71). Baseline no treatment: 39.67 (11.34).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 5, Reason: 5 lost to follow up

Protocol outcome 5: Pain at </=3 months - Actual outcome: WOMAC pain at 3 months; Group 1: mean 10.34 (SD 4.12); n=80, Group 2: mean 11.89 (SD 4.29); n=80; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure: 15.31 (8.24). Baseline no treatment: 13.16 (5.25). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 5, Reason: 5 lost to follow up Protocol outcome 6: Pain at > 3 months - Actual outcome: WOMAC pain at 12 months; Group 1: mean 8.54 (SD 3.33); n=75, Group 2: mean 10.23 (SD 6.23); n=75; WOMAC pain 0-20 Top=High is poor outcome; Comments: Baseline acupressure: 15.31 (8.24). Baseline no treatment: 13.16 (5.25). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 5 lost to follow up; Group 2 Number missing: 5, Reason: 5 lost to follow up	
Protocol outcomes not reported by the study	Psychological distress at </=3 months; Psychological distress at > 3 months; Osteoarthritis flares at </=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at </=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at </=3 months; Moderate/major adverse events at > 3 months

Study	Villafane 2013[105]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Italy; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: Intervention 4 weeks + 2 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis established by a hand surgeon. Each patient underwent subjective and physical examination, performed by a physical physiotherapist experienced in musculoskeletal physiotherapy and was evaluated for inclusion/exclusion in the study. A diagnosis of stage III or IV secondary CMC joint OA in the dominant hand, according to the Eaton-Littler-Burton classification system based on radiographic findings was required.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	A history of repetitive use of their dominant hand (e.g. former factory worker) and a diagnosis of stage III or IV secondary CMC joint OA in the dominant hand, according to the Eaton-Littler-Burton classification system based on radiographic findings.
Exclusion criteria	Scoring greater than 4 points on the Beck Depression Inventory or greater than 30 points on the State-Trait Anxiety Inventory. Patients with a medical history of carpal tunnel syndrome, surgical interventions to the first CMC joint, De Quervain tenosynovitis, bilateral symptoms, or degenerative or nondegenerative neurological conditions in which pain perception was altered.
Recruitment/selection of patients	From January 2012 to April 2012.
Age, gender and ethnicity	Age - Mean (SD): 82 (6) years. Gender (M:F): 9:51. Ethnicity: Not stated.
Further population details	1. Age: > 75 years 2. Diagnosis with or without imaging: Diagnosis with imaging 3. Multimorbidity: Not stated / Unclear 4. Site of osteoarthritis: Thumb osteoarthritis
Extra comments	Severity: pain: 5.0 (0.3) versus 5.0 (0.2). Duration of pain: not stated. Participants were asked not to take analgesics, muscle relaxants, or anti-inflammatory drugs for 24 hours prior to the examination. None of the individuals had received prior interventions for CMC joint OA, and were therefore naive to the treatment they received.
Indirectness of population	No indirectness

Interventions	(n=30) Intervention 1: Manual therapy and exercise combined - Combined active and passive manual therapy and exercise. Joint mobilisation, Neurodynamic intervention and exercise: A grade 3 posterior/anterior glide with distraction technique to the first CMC joint. The therapist grasped the right-thumb and index finger and distracted the joint, retracting the thumb and gliding the first metacarpal bone in a posterior/anterior direction. Neurodynamic techniques involved a passive 'nerve slider' neurodynamic technique purported to bias the median nerve, was applied. They used a protocol-based treatment approach, standardising the interventions for all included patients, rather than an impairment-based approach. Exercise: patients received received the same standardised exercise protocol as that described by Rogers and Wilder. The first 6 exercises consisted of active range-of-motion movements of the hand that were designed to improve joint flexibility. The remaining 3 exercises were designed to strengthen grip and pinch strength by using a non-latex polymer ball hand exerciser. . Duration 12 sessions over 4 weeks (3 sessions per week). Joint mobilisation applied for 3 minutes with 1 minute rest period, repeated 3 times. Neurodynamic nerve slider technique was performed twice for 5 minutes each time, with a 1-minute rest between sets. The polymer ball involved 10 repetitions for the first 4 sessions, progressed to 12 repetitions for the next 2 sessions, then to 15 repetitions for 2 sessions, and finally 20, if able for the last 4 sessions. . Concurrent medication/care: Not stated.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Mobilisation/manipulation (n=30) Intervention 2: Sham manual therapy. Placebo group received the same number of treatment sessions of a similar duration as those in the experimental group, but received only in-active doses of pulsed ultrasound with an intensity of 0 W/cm2 and gentle application of an inert gel for 10 minutes to the hypothenar areas of the symptomatic hand. . Duration Similar to experimental group. . Concurrent medication/care: Not stated.. Indirectness: No indirectness Further details: 1. Type of manual intervention: Not applicable
Funding	No funding (Funded by lead Author.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINED ACTIVE AND PASSIVE MANUAL THERAPY AND EXERCISE versus SHAM MANUAL THERAPY

Protocol outcome 1: Pain at ≤/=3 months
- Actual outcome: Pain at 2 months post-intervention; Group 1: mean 1.5 (SD 0.2); n=30, Group 2: mean 4.4 (SD 0.3); n=30; Pain VAS 1-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain (VAS) mean(SD): experimental group 5.0 (0.3); placebo group 5.0 (0.2).; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health related quality of life at ≤/=3 months; Health related quality of life at > 3 months; Physical function at ≤/=3 months; Physical function at > 3 months; Pain at > 3 months; Psychological distress at ≤/=3 months; Psychological distress at > 3 months; Osteoarthritis flares at ≤/=3 months; Osteoarthritis flares at > 3 months; Minor adverse events at ≤/=3 months; Minor adverse events at > 3 months; Moderate/major adverse events at ≤/=3 months; Moderate/major adverse events at > 3 months

Appendix E – Forest plots

E.1 Manual therapy versus sham therapy

Figure 2: Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months

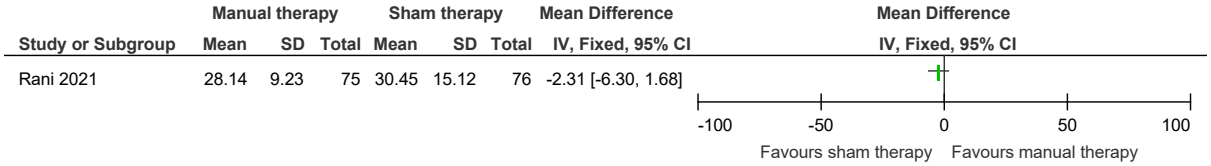


Figure 3: Quality of life (SF-36 mental component, 0-100, high is good, final value) at ≤3 months

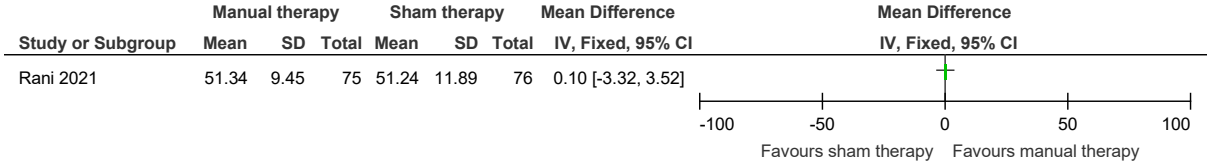


Figure 4: Quality of life (SF-36 physical component, 0-100, high is good, final value) at >3 months

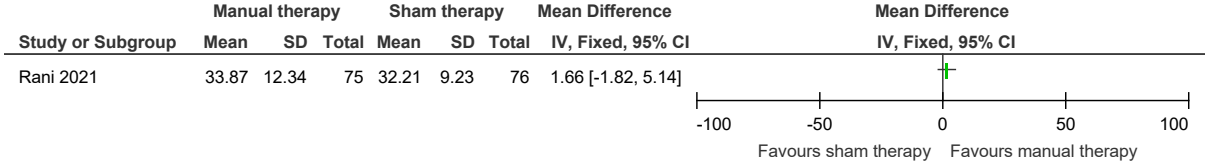


Figure 5: Quality of life (SF-36 mental component, 0-100, high is good, final value) at >3 months

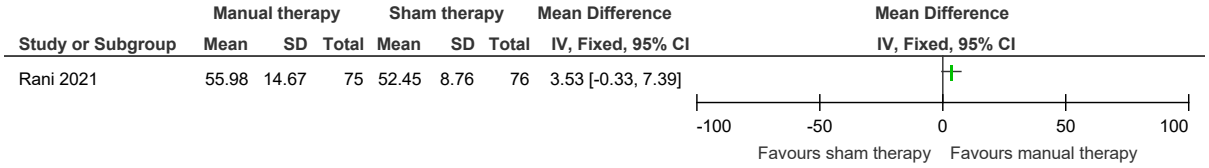


Figure 6: Pain (WOMAC, NRS [different scale ranges], high is poor, final values) at ≤3 months

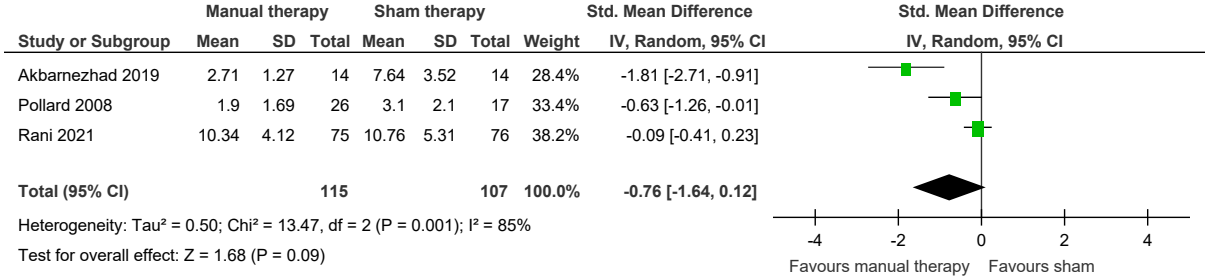


Figure 7: Pain (WOMAC, 0-20, high is poor, final value) at >3 months

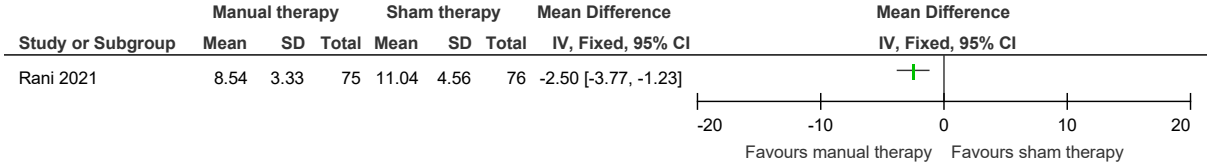


Figure 8: Physical function (WOMAC [different scale ranges], high is poor, final value) at ≤3 months

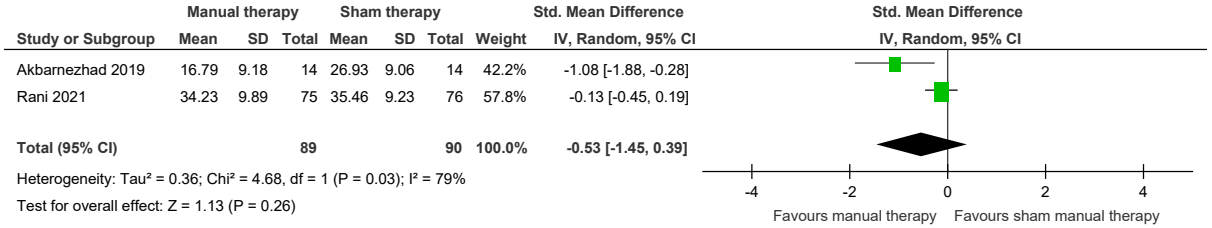
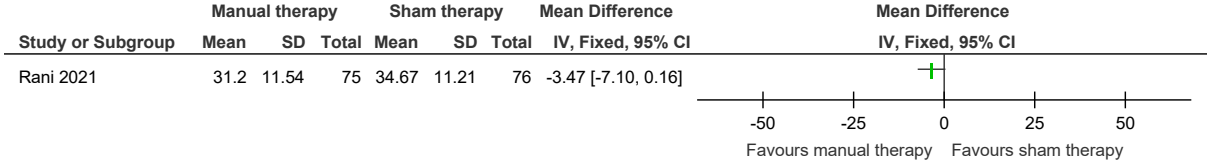


Figure 9: Physical function (WOMAC, 0-68, high is poor, final value) at >3 months



E.2 Manual therapy versus no treatment

Figure 10: Quality of life (SF-6D, 6-31, high is poor, final value) at ≤3 months

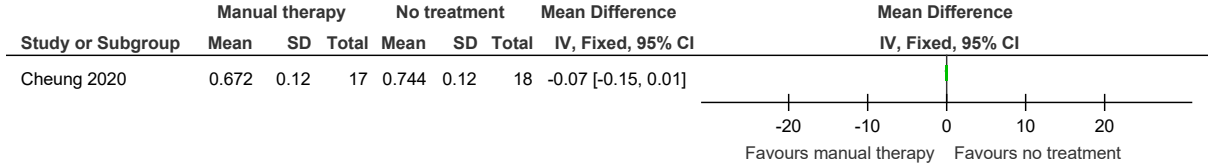


Figure 11: Quality of life (SF-36 physical component summary, 0-100, high is good, final value) at ≤3 months

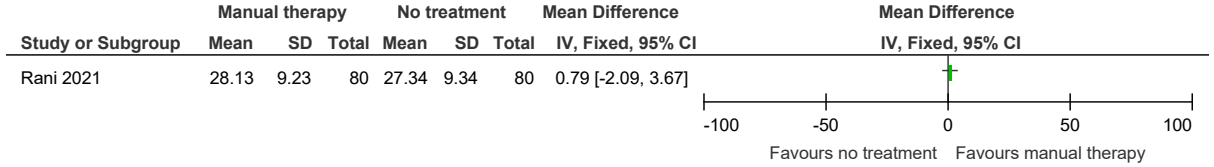


Figure 12: Quality of life (SF-36 mental component summary, 0-100, high is good, final value) at ≤3 months

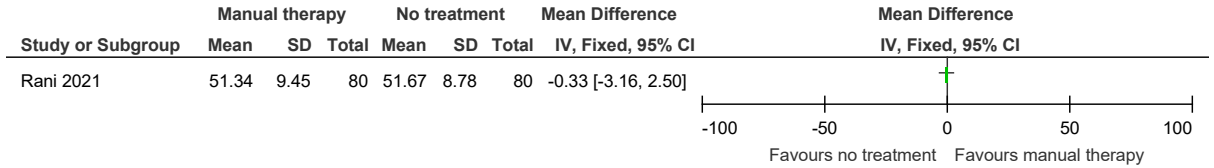


Figure 13: Quality of life (SF-36 physical component summary, 0-100, high is good, final value) at >3 months

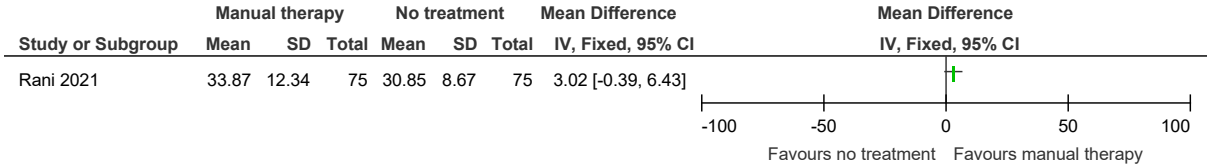


Figure 14: Quality of life (SF-36 mental component summary, 0-100, high is good, final value) at >3 months

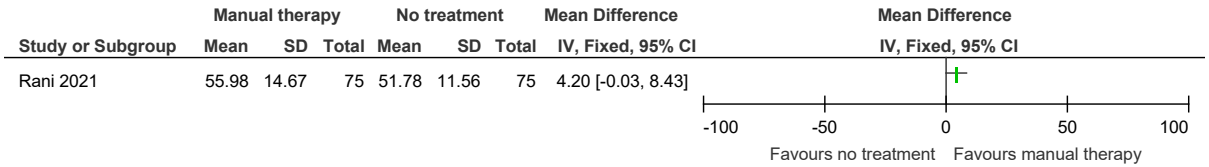


Figure 15: Pain (WOMAC [different scale ranges], high is poor, final values) at ≤3 months

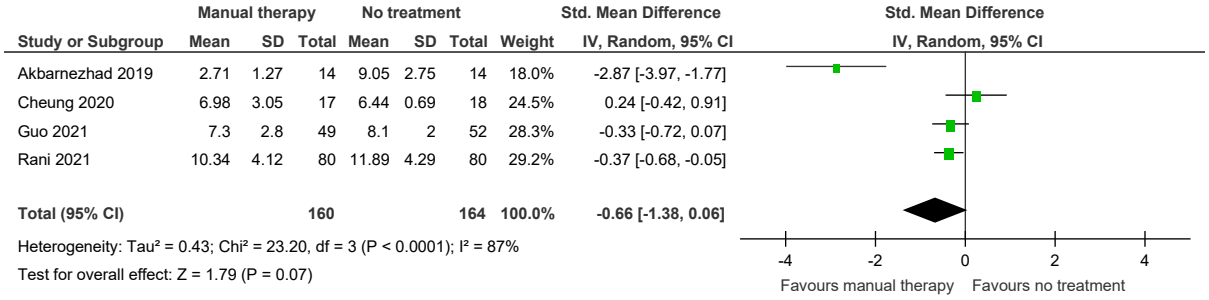


Figure 16: Pain (NRS, 0-10, high is poor, change score and final value) at at ≤3 months

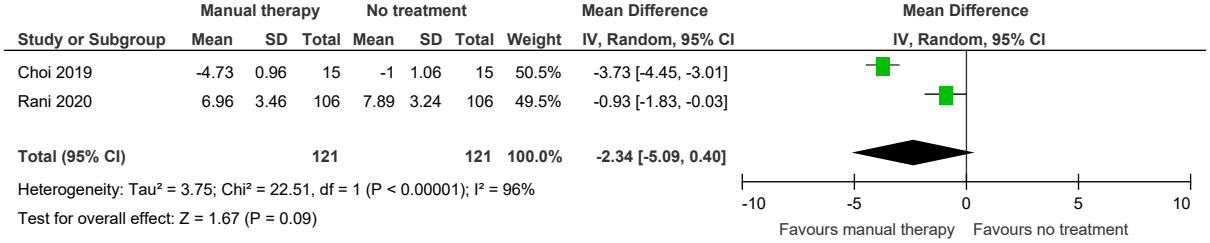


Figure 17: Pain (NRS, 0-10, high is poor, change scores) at >3 months

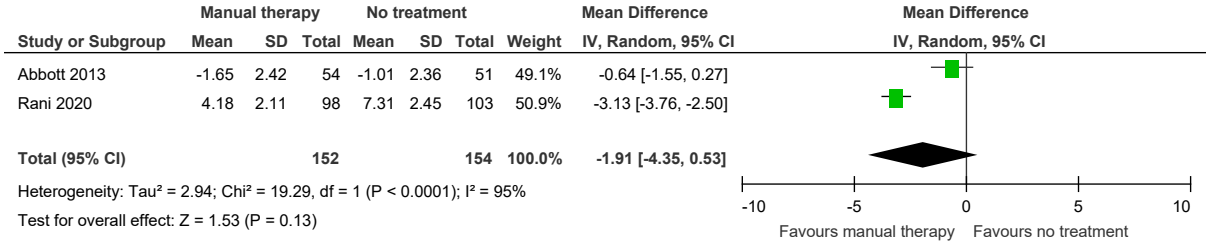


Figure 18: Pain (WOMAC, 0-20, high is poor, final values) at >3 months

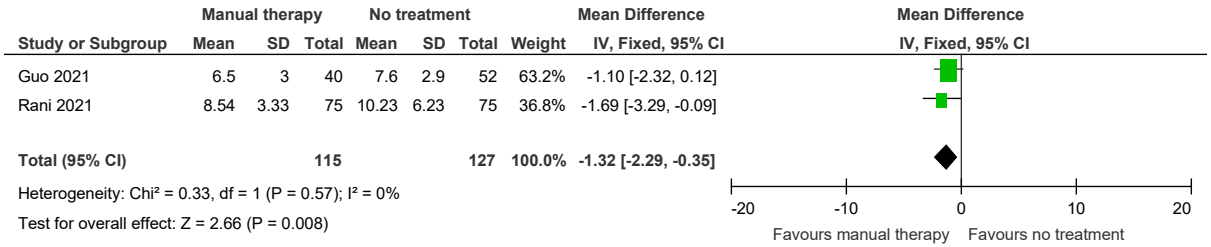


Figure 19: Physical function (WOMAC, 0-68, high is poor, change score) at ≤3 months

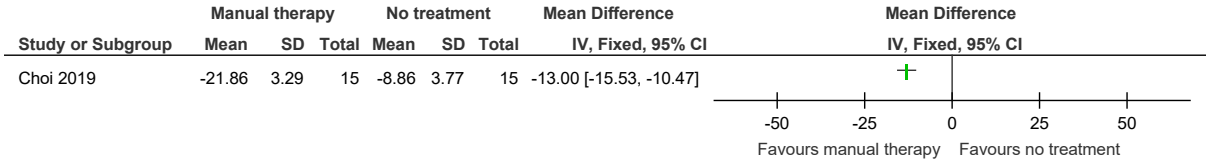


Figure 20: Physical function (WOMAC [different scale ranges], high is poor, final values) at ≤3 months

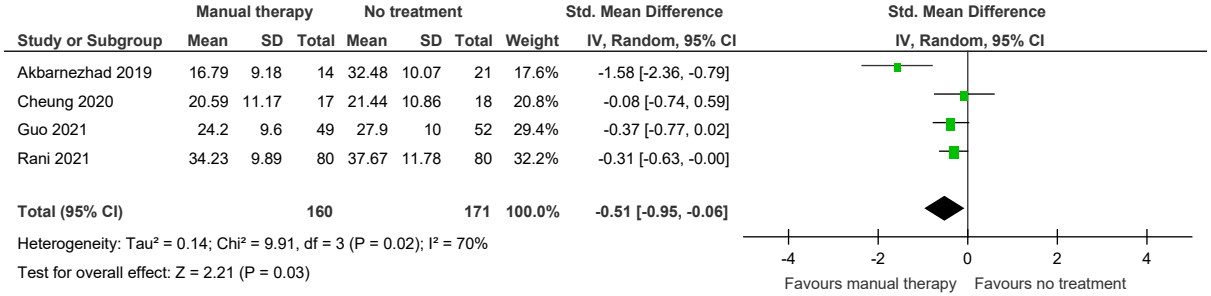


Figure 21: Physical function (WOMAC, 0-68, high is poor, final values) at >3 months

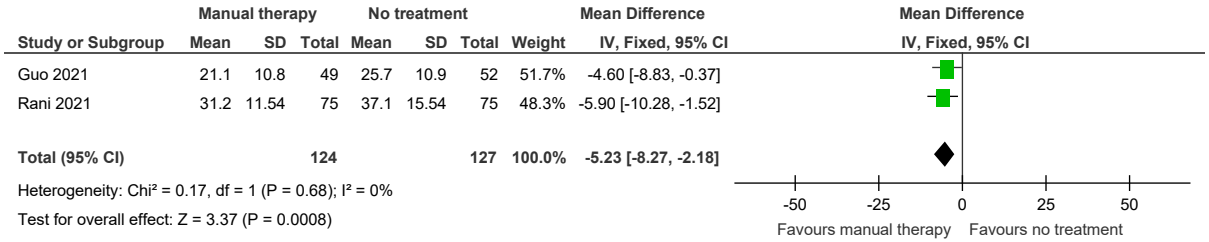


Figure 22: Psychological distress (BDI, 0-63, high is poor, change score) at ≤3 months

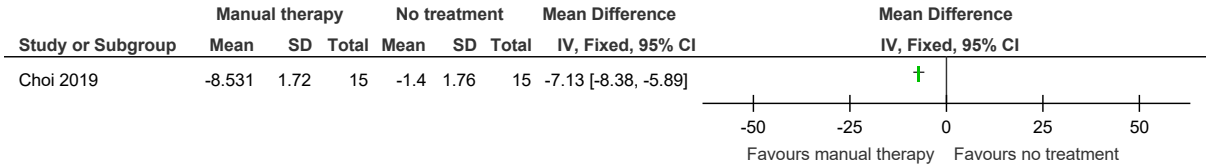


Figure 23: Psychological distress (DASS-21 depression, 0-21, high is poor, final value) at ≤3 months

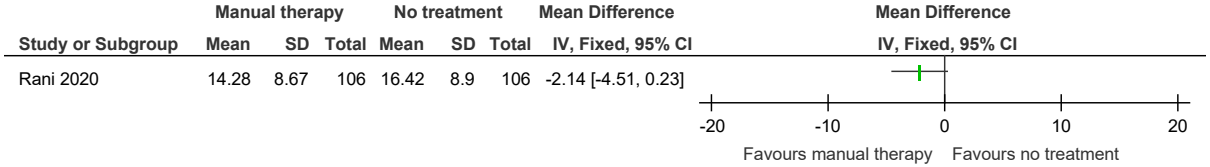


Figure 24: Psychological distress (DASS-21 anxiety, 0-21, high is poor, final value) at ≤3 months

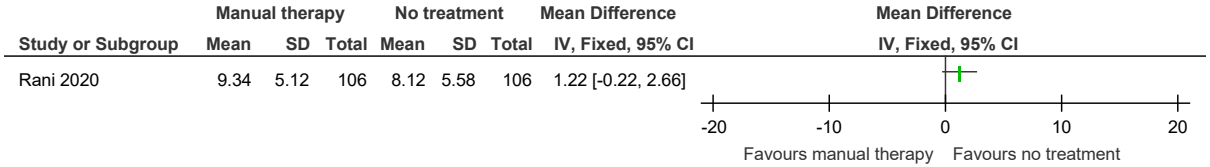


Figure 25: Psychological distress (DASS-21 stress, 0-21, high is poor, final value) at ≤3 months

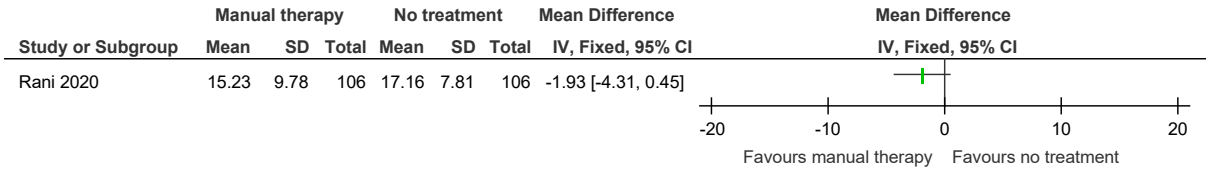


Figure 26: Psychological distress (DASS-21 depression, 0-21, high is poor, final value) at >3 months

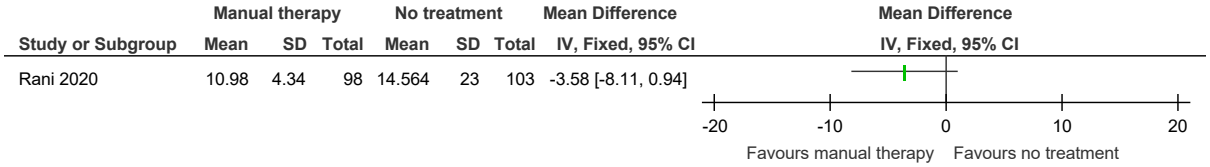


Figure 27: Psychological distress (DASS-21 anxiety, 0-21, high is poor, final value) at >3 months

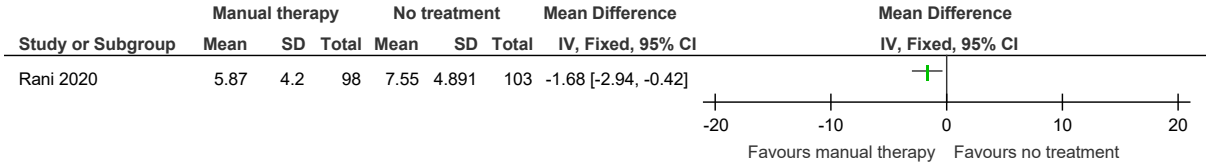


Figure 28: Psychological distress (DASS-21 stress, 0-21, high is poor, final value) at >3 months

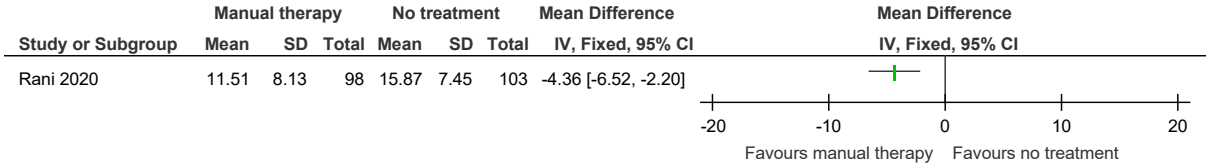


Figure 29: Minor adverse events at at ≤3 months

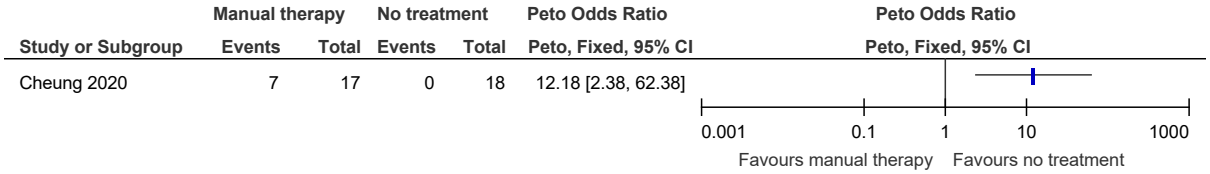


Figure 30: Moderate/major adverse events at >3 months

E.3 Manual therapy and exercise versus exercise

Figure 31: Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months

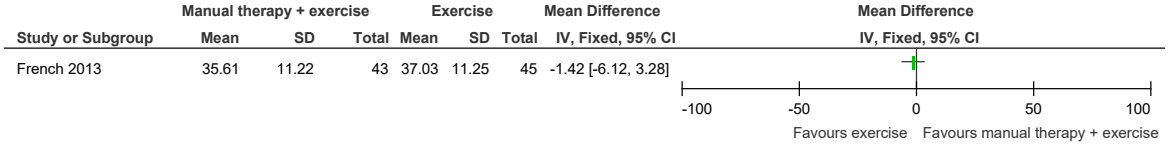


Figure 32: Quality of life (SF-36 mental component, 0-100, high is good, final value) at ≤3 months

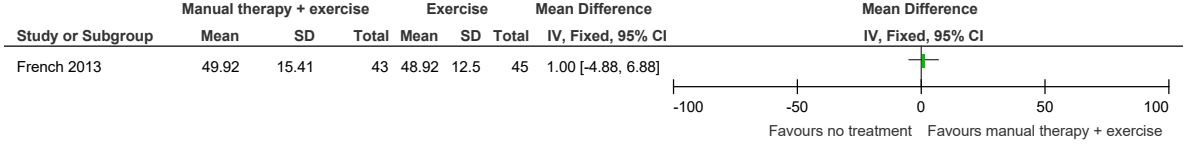


Figure 33: Pain (VAS, 0-10, high is poor, change score) at ≤3 months

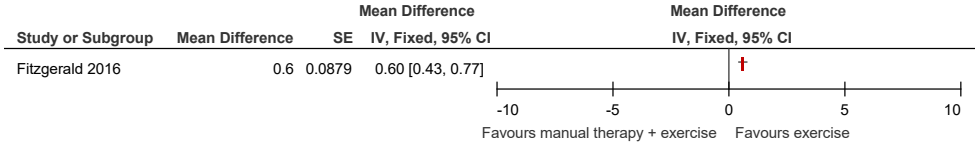


Figure 34: Pain (WOMAC, NRS [different scale ranges], high is poor, final values) at ≤3 months

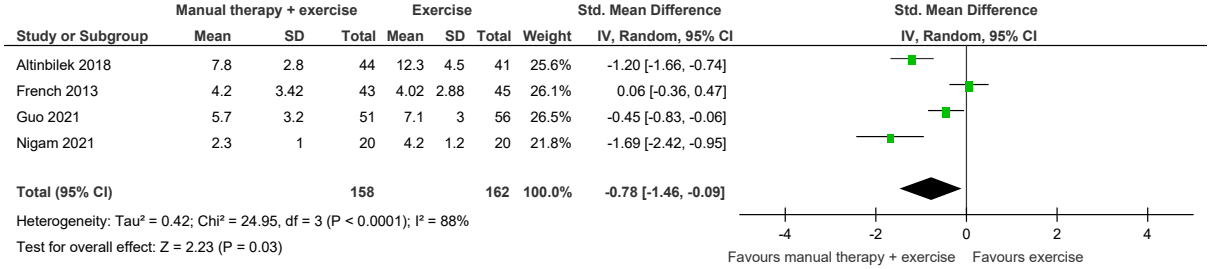


Figure 35: Pain (VAS, 0-10, high is poor, change scores and final values) at >3 months

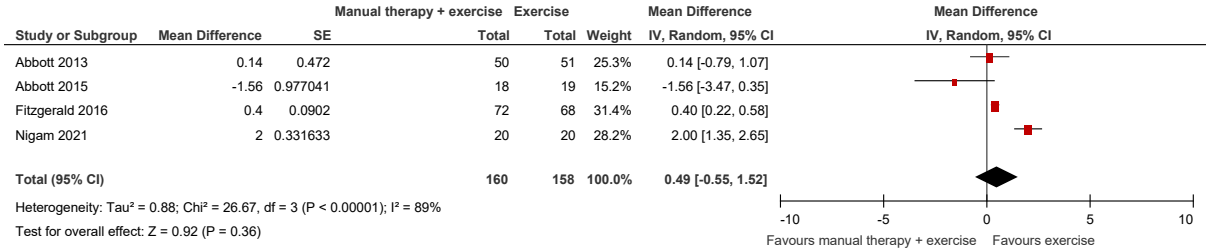


Figure 36: Pain (WOMAC, 0-20, high is poor, final value) at >3 months

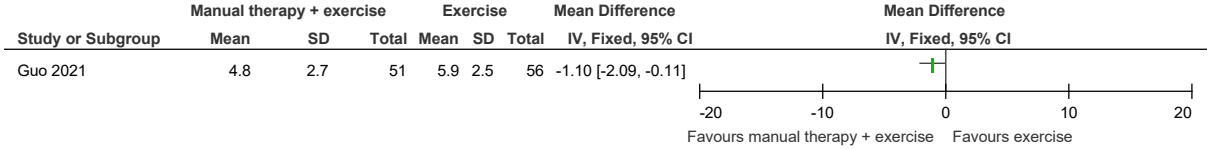


Figure 37: Physical function (WOMAC [different scale ranges], high is poor, final values) at ≤3 months

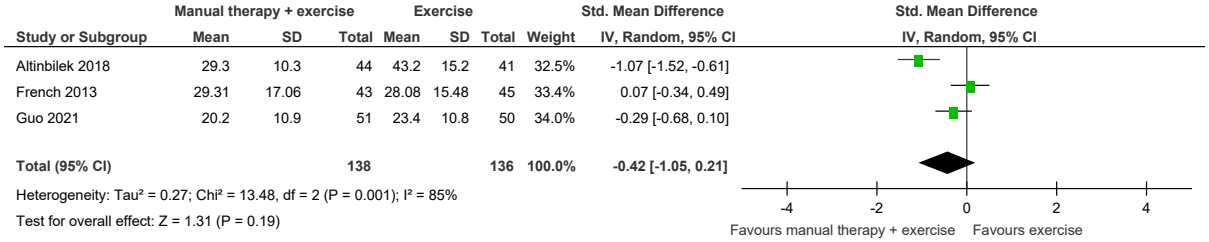


Figure 38: Physical function (WOMAC, 0-68, high is poor, final value) at >3 months

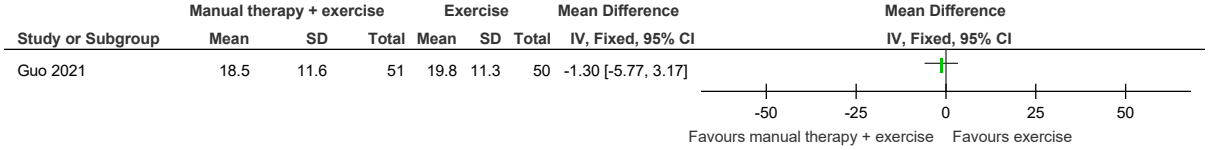


Figure 39: Psychological distress (HADS anxiety subscale, 0-21, high is poor, final value) at ≤3 months

	Manual therapy + exercise			Exercise			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
French 2013	6.31	5.54	43	6.74	4.27	45	-0.43 [-2.50, 1.64]	

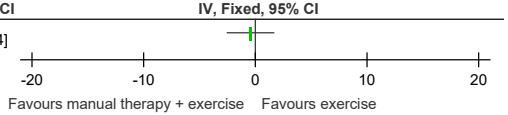


Figure 40: Psychological distress (HADS depression subscale, 0-21, high is poor, final value) at ≤3 months

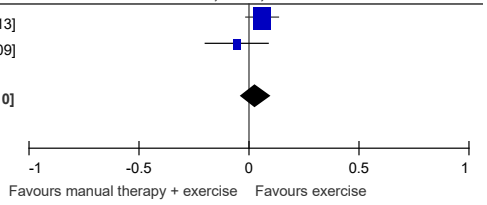
	Manual therapy + exercise			Exercise			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
French 2013	4.83	4.63	43	5.02	3.39	45	-0.19 [-1.89, 1.51]	

Figure 41: Adverse events at >3 months

	Favours manual therapy + exercise		Exercise			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Abbott 2013	3	50	0	51	74.3%	0.06 [-0.01, 0.13]	
Abbott 2015	0	17	1	18	25.7%	-0.06 [-0.20, 0.09]	
Total (95% CI)		**67**		**69**	**100.0%**	**0.03 [-0.04, 0.10]**	
Total events	3		1				

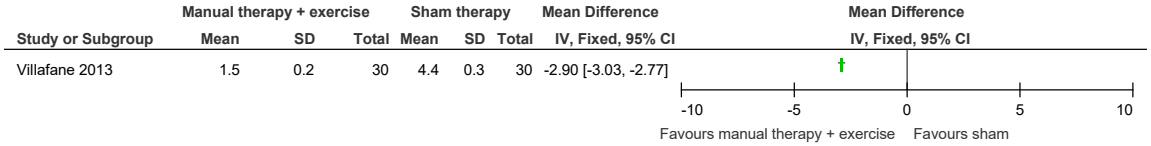
Heterogeneity: Chi² = 2.00, df = 1 (P = 0.16); I² = 50%

Test for overall effect: Z = 0.87 (P = 0.39)



E.4 Manual therapy and exercise versus sham therapy

Figure 42: Pain (VAS, 1-10, high is poor, final value) at ≤3 months



E.5 Manual therapy and exercise versus no treatment

Figure 43: Quality of life (SF-36 physical component, 0-100, high is good, final value) at ≤3 months

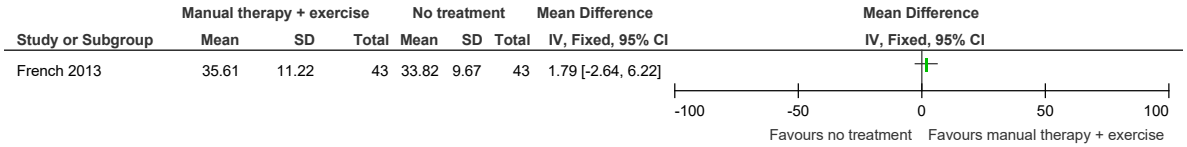


Figure 44: Quality of life (SF-36 mental component, 0-100, high is good, final value) at ≤3 months

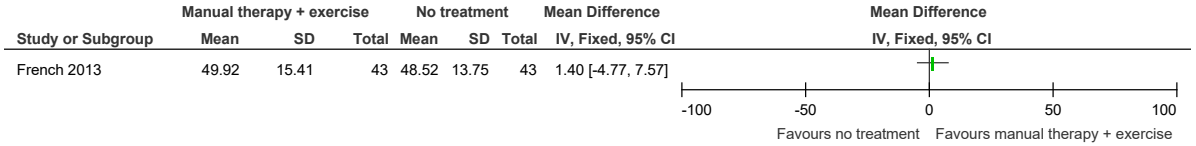


Figure 45: Quality of life (EQ-5D, 0-1, high is good, adjusted final score) at >3 months

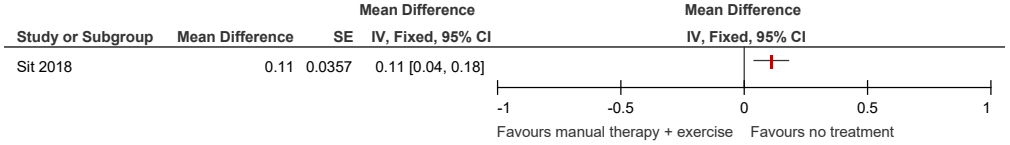


Figure 46: Pain (WOMAC, NRS [different scale ranges], high is poor, final value) at ≤3 months

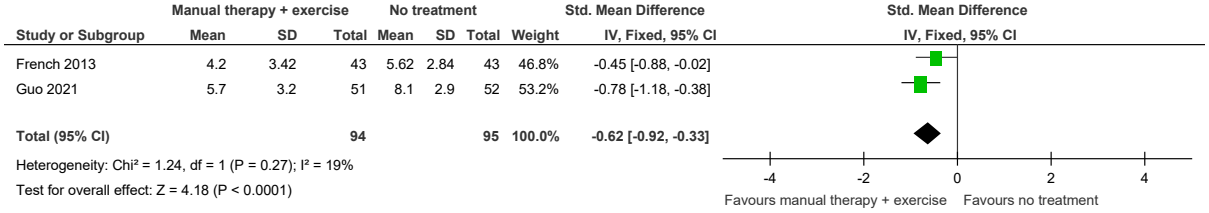


Figure 47: Pain (WOMAC, VAS, 0-100, high is poor, change score and adjusted final score) at >3 months

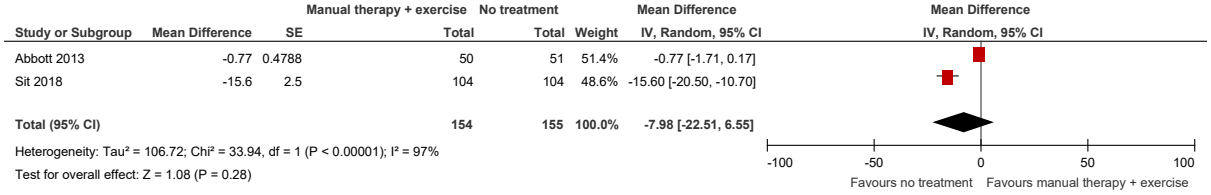


Figure 48: Pain (WOMAC, 0-20, high is poor, final value) at >3 months

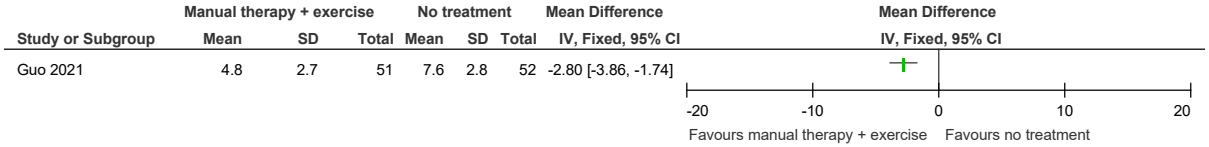


Figure 49: Physical function (WOMAC, 0-68, high is poor, final values) at ≤3 months

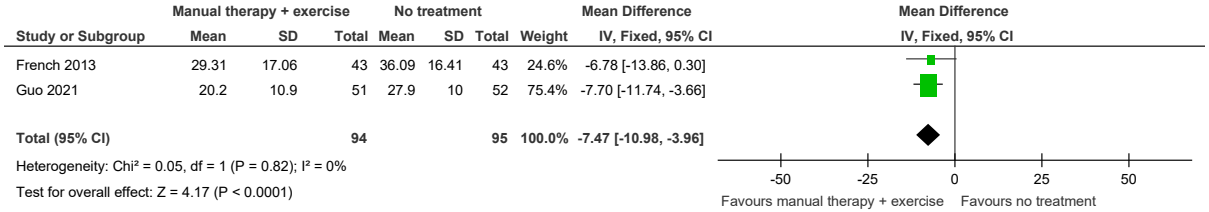


Figure 50: Physical function (WOMAC, 0-100, high is poor, adjusted final score) at >3 months

Figure 51: Psychological distress (HADS anxiety subscale, 0-21, high is poor, final value) at ≤3 months

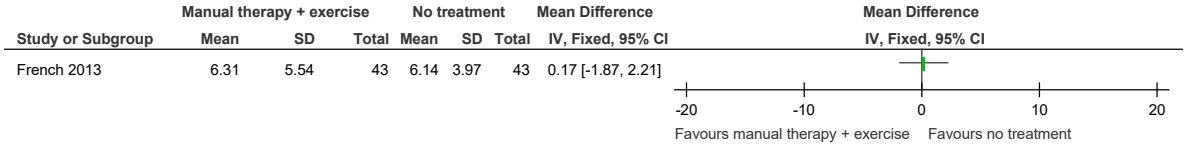


Figure 52: Psychological distress (HADS depression subscale, 0-21, high is poor, final value) ≤3 months

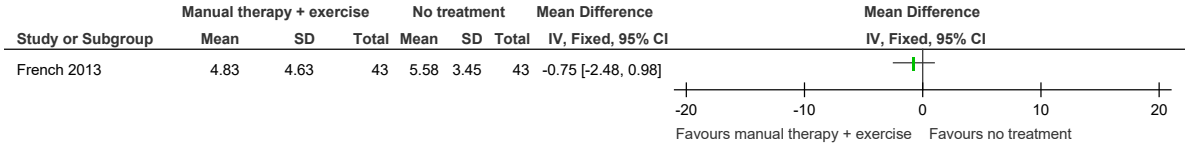
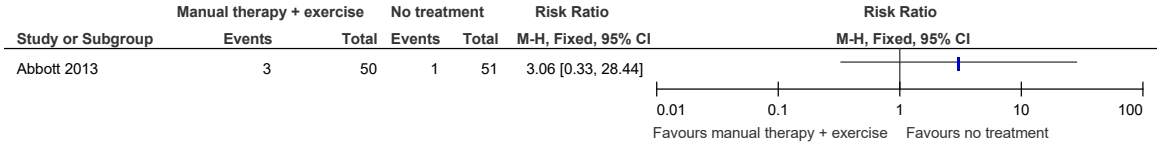


Figure 53: Moderate/major adverse events at >3 months



Appendix F – GRADE tables

Table 10: Clinical evidence profile: manual therapy versus no treatment for osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy	no treatment	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-6D, 6-31, high is poor, final value) at <3 months (follow-up: 6 weeks; assessed with: SF-6D; Scale from: 6 to 31)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17	18	-	MD **0.07 lower** (0.15 lower to 0.01 higher)	⨁⨁◯◯ Low	CRITICAL
Quality of life (SF-36 physical component summary, 0-100, high is good, final value) at <3 months (follow-up: 3 months; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	80	80	-	MD **0.79 higher** (2.09 lower to 3.67 higher)	⨁⨁◯◯ Low	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, final value) at <3 months (follow-up: 3 months; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	80	80	-	MD **0.33 lower** (3.16 lower to 2.5 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Quality of life (SF-36 physical component summary, 0-100, high is good, final value) at >3 months (follow-up: 12 months; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	75	75	-	MD **3.02 higher** (0.39 lower to 6.43 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, final value) at >3 months (follow-up: 12 months; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	75	75	-	MD **4.2 higher** (0.03 lower to 8.43 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy	no treatment	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC [different scale ranges], high is poor, final values) at <3 months (follow-up: mean 8 weeks; assessed with: WOMAC)												
4	randomised trials	serious[a]	very serious[c]	not serious	serious[b]	none	160	164	-	SMD **0.66 SD lower** (1.38 lower to 0.06 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (NRS, 0-10, high is poor, change score and final value) at <3 months (follow-up: mean 6 weeks; assessed with: NRS)												
2	randomised trials	very serious[a]	very serious[c]	not serious	serious[b]	none	121	121	-	MD **2.34 lower** (5.09 lower to 0.4 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (NRS, 0-10, high is poor, change scores) at >3 months (follow-up: mean 16 months; assessed with: NRS; Scale from: 0 to 10)												
2	randomised trials	very serious[a]	very serious[c]	not serious	serious[b]	none	152	154	-	MD **1.91 lower** (4.35 lower to 0.53 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (WOMAC, 0-20, high is poor, final value) at >3 months (follow-up: 12 months; assessed with: WOMAC; Scale from: 0 to 20)												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	115	127	-	MD **1.32 lower** (2.29 lower to 0.35 lower)	⨁⨁◯◯ Low	CRITICAL
Physical function (WOMAC, 0-68, high is poor, change score) at <3 months (follow-up: 4 weeks; assessed with: WOMAC; Scale from: 0 to 68)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	15	15	-	MD **13 lower** (15.53 lower to 10.47 lower)	⨁⨁◯◯ Low	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, final values) at <3 months (follow-up: mean 8 weeks; assessed with: WOMAC)												
4	randomised trials	serious[a]	very serious[c]	not serious	serious[b]	none	160	171	-	SMD **0.51 SD lower** (0.95 lower to 0.06 lower)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy	no treatment	Relative (95% CI)	Absolute (95% CI)		
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months (follow-up: 12 months; assessed with: WOMAC; Scale from: 0 to 68)												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	124	127	-	MD **5.23 lower** (8.27 lower to 2.18 lower)	⨁⨁◯◯ Low	CRITICAL
Psychological distress (BDI, 0-63, high is poor, change score) at <3 months (follow-up: 4 weeks; assessed with: BDI; Scale from: 0 to 63)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	15	15	-	MD **7.13 lower** (8.38 lower to 5.89 lower)	⨁⨁◯◯ Low	IMPORTANT
Psychological distress (DASS-21 depression, 0-21, high is poor, final value) at <3 months (follow-up: 2 months; assessed with: DASS-21 depression; Scale from: 0 to 21)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	106	106	-	MD **2.14 lower** (4.51 lower to 0.23 higher)	⨁◯◯◯ Very low	IMPORTANT
Psychological distress (DASS-21 anxiety, 0-21, high is poor, final value) at <3 months (follow-up: 2 months; assessed with: DASS-21 anxiety; Scale from: 0 to 21)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	106	106	-	MD **1.22 higher** (0.22 lower to 2.66 higher)	⨁⨁◯◯ Low	IMPORTANT
Psychological distress (DASS-21 stress, 0-21, high is poor, final value) at <3 months (follow-up: 2 months; assessed with: DASS-21 stress; Scale from: 0 to 21)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	106	106	-	MD **1.93 lower** (4.31 lower to 0.45 higher)	⨁⨁◯◯ Low	IMPORTANT
Psychological distress (DASS-21 depression, 0-21, high is poor, final value) at >3 months (follow-up: 8 months; assessed with: DASS-21 depression; Scale from: 0 to 21)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	106	106	-	MD **3.58 lower** (8.11 lower to 0.94 higher)	⨁⨁◯◯ Low	IMPORTANT
Psychological distress (DASS-21 anxiety, 0-21, high is poor, final value) at >3 months (follow-up: 8 months; assessed with: DASS-21 anxiety; Scale from: 0 to 21)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	106	106	-	MD **1.68 lower** (2.94 lower to 0.42 lower)	⨁◯◯◯ Very low	IMPORTANT
Psychological distress (DASS-21 stress, 0-21, high is poor, final value) at >3 months (follow-up: 8 months; assessed with: DASS-21 stress; Scale from: 0 to 21)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	106	106	-	MD **4.36 lower** (6.52 lower to 2.2 lower)	⨁◯◯◯ Very low	IMPORTANT
Minor adverse events at <3 months (follow-up: 6 weeks)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	7/17 (41.2%)	0/18 (0.0%)	**OR 12.18** (2.38 to 62.38)	**410 more per 1,000** (from 170 more to 650 more)[d]	⨁⨁⨁◯ Moderate	IMPORTANT
Moderate/major adverse events at >3 months (follow-up: 12 months)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	0/54 (0.0%)	1/51 (2.0%)	**Peto OR 0.13** (0.00 to 6.44)	**20 fewer per 1,000** (from 70 fewer to 30 more)[d]	⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 11: Clinical evidence profile: manual therapy and exercise versus exercise for osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy and exercise	exercise	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 physical component, 0-100, high is good, final value) at <3 months (follow-up: 9 weeks; assessed with: SF-36 physical component; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	43	45	-	MD **1.42 lower** (6.12 lower to 3.28 higher)	⨁◯◯◯ Very low	CRITICAL
Quality of life (SF-36 mental component, 0-100, high is good, final value) <3 months (follow-up: 9 weeks; assessed with: SF-36 mental component; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	43	45	-	MD **1 higher** (4.88 lower to 6.88 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (VAS, 0-10, high is poor, change scores) at <3 months (follow-up: 9 weeks; assessed with: VAS; Scale from: 0 to 10)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	75	75	-	MD **0.6 higher** (0.43 higher to 0.77 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (WOMAC, NRS [different scale ranges], high is poor, final values) at <3 months (follow-up: mean 8 weeks)												
4	randomised trials	serious[a]	very serious[c]	not serious	serious[b]	none	158	162	-	SMD **0.78 SD lower** (1.46 lower to 0.09 lower)	⨁◯◯◯ Very low	CRITICAL
Pain (VAS, 0-10, high is poor, change scores) at >3 months (follow-up: mean 14 months; assessed with: VAS; Scale from: 0 to 10)												
4	randomised trials	serious[a]	very serious[c]	not serious	serious[b]	none	160	158	-	MD **0.49 higher** (0.55 lower to 1.52 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (WOMAC, 0-20, high is poor, final value) at >3 months (follow-up: 16 weeks; assessed with: WOMAC; Scale from: 0 to 20)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	51	56	-	MD **1.1 lower** (2.09 lower to 0.11 lower)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy and exercise	exercise	Relative (95% CI)	Absolute (95% CI)		
Physical function (WOMAC [different scale ranges], high is poor, final values) at <3 months (follow-up: mean 7 weeks; assessed with: WOMAC)												
3	randomised trials	serious[a]	very serious[c]	not serious	serious[b]	none	138	136	-	SMD **0.42 SD lower** (1.05 lower to 0.21 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months (follow-up: 16 weeks; assessed with: WOMAC; Scale from: 0 to 68)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	51	50	-	MD **1.3 lower** (5.77 lower to 3.17 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Psychological distress (HADS anxiety subscale, 0-21, high is poor, final value) at <3 months (follow-up: 9 weeks; assessed with: HADS anxiety subscale; Scale from: 0 to 21)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	43	45	-	MD **0.43 lower** (2.5 lower to 1.64 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Psychological distress (HADS depression subscale, 0-21, high is poor, final value) <3 months (follow-up: 9 weeks; assessed with: HADS depression subscale; Scale from: 0 to 21)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	43	45	-	MD **0.19 lower** (1.89 lower to 1.51 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Moderate/major adverse events at >3 months (follow-up: mean 12 months)												
2	randomised trials	not serious	serious[d]	not serious	serious[b]	none	3/67 (4.5%)	1/69 (1.4%)	**OR 2.84** (0.39 to 20.50)	**30 more per 1,000** (from 40 fewer to 100 more)[e]	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 12: Clinical evidence profile: manual therapy and exercise versus sham therapy for osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy and exercise	sham therapy	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 1-10, high is poor, final value) at ≤3 months (follow up: 8 weeks; assessed with: VAS; Scale from: 1 to 10)												
1	randomised trials	not serious	not serious	not serious	not serious	none	30	30	-	MD **2.9 lower** (3.03 lower to 2.77 lower)	⨁⨁⨁⨁ High	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Table 13: Clinical evidence profile: manual therapy and exercise versus no treatment for osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy and exercise	no treatment	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 physical component, 0-100, high is good, final value) at <3 months (follow-up: 9 weeks; assessed with: SF-36 physical component; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	43	43	-	MD **1.79 higher** (2.64 lower to 6.22 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy and exercise	no treatment	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 mental component, 0-100, high is good, final value) <3 months (follow-up: 9 weeks; assessed with: SF-36 mental component; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	43	43	-	MD **1.4 higher** (4.77 lower to 7.57 higher)	⨁◯◯◯ Very low	CRITICAL
Quality of life (EQ-5D, 0-1, high is good, adjusted final score) at >3 months (follow-up: 24 weeks; assessed with: EQ-5D; Scale from: 0 to 1)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	104	104	-	MD **0.11 higher** (0.04 higher to 0.18 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (WOMAC, NRS [different scale ranges], high is poor, final value) at <3 months (follow-up: mean 9 weeks; assessed with: WOMAC, NRS)												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	94	95	-	SMD **0.62 SD lower** (0.92 lower to 0.33 lower)	⨁⨁◯◯ Low	CRITICAL
Pain (WOMAC, VAS, 0-100, high is poor, change score and adjusted final score) at >3 months (follow-up: mean 64 weeks; assessed with: WOMAC, VAS; Scale from: 0 to 100)												
2	randomised trials	serious[a]	very serious[c]	not serious	very serious[b]	none	154	155	-	MD **7.98 lower** (22.51 lower to 6.55 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (WOMAC, 0-20, high is poor, final value) at >3 months (follow-up: 16 weeks; assessed with: WOMAC; Scale from: 0 to 20)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	51	52	-	MD **2.8 lower** (3.86 lower to 1.74 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function (WOMAC, 0-68, high is poor, final value) at <3 months (follow-up: mean 9 weeks; assessed with: WOMAC; Scale from: 0 to 68)												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	94	95	-	MD **7.47 lower** (10.98 lower to 3.96 lower)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy and exercise	no treatment	Relative (95% CI)	Absolute (95% CI)		
Physical function (WOMAC, 0-100, high is poor, adjusted final values) at >3 months (follow-up: mean 20 weeks; assessed with: WOMAC; Scale from: 0 to 100)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	155	156	-	SMD **0.75 SD lower** (0.98 lower to 0.52 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Psychological distress (HADS anxiety subscale, 0-21, high is poor, final value) at <3 months (follow-up: 9 weeks; assessed with: HADS anxiety subscale; Scale from: 0 to 21)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	43	43	-	MD **0.17 higher** (1.87 lower to 2.21 higher)	⨁⨁◯◯ Low	IMPORTANT
Psychological distress (HADS depression subscale, 0-21, high is poor, final value) <3 months (follow-up: 9 weeks; assessed with: HADS depression subscale; Scale from: 0 to 21)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	43	43	-	MD **0.75 lower** (2.48 lower to 0.98 higher)	⨁◯◯◯ Very low	IMPORTANT
Moderate/major adverse events at >3 months (follow-up: 12 months)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	3/50 (6.0%)	1/51 (2.0%)	**RR 3.06** (0.33 to 28.44)	**40 more per 1,000** (from 13 fewer to 538 more)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

Table 14: Clinical evidence profile: manual therapy versus sham therapy for osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy	sham therapy	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 physical component, 0-100, high is good, final value) at <3 months (follow-up: 3 months; assessed with: SF-36 physical component; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	75	76	-	MD **2.31 lower** (6.3 lower to 1.68 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Quality of life (SF-36 mental component, 0-100, high is good, final value) at <3 months (follow-up: 3 months; assessed with: SF-36 mental component; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	75	76	-	MD **0.1 higher** (3.32 lower to 3.52 higher)	⨁⨁◯◯ Low	CRITICAL
Quality of life (SF-36 physical component, 0-100, high is good, final value) at >3 months (follow-up: 12 months; assessed with: SF-36 physical component; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	75	76	-	MD **1.66 higher** (1.82 lower to 5.14 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Quality of life (SF-36 mental component, 0-100, high is good, final value) at >3 months (follow-up: 12 months; assessed with: SF-36 mental component; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	75	76	-	MD **3.53 higher** (0.33 lower to 7.39 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (WOMAC, NRS [different scale ranges], high is poor, final values) at <3 months (follow-up: mean 6 weeks; assessed with: WOMAC, NRS)												
3	randomised trials	not serious	very serious[b]	not serious	serious[a]	none	115	107	-	SMD **0.76 SD lower** (1.64 lower to 0.12 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (WOMAC, 0-20, high is poor, final value) at >3 months (follow-up: 12 months; assessed with: WOMAC; Scale from: 0 to 20)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy	sham therapy	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	75	76	-	MD **2.5 lower** (3.77 lower to 1.23 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, final value) at <3 months (follow-up: mean 8 weeks; assessed with: WOMAC)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	89	90	-	SMD **0.53 SD lower** (1.45 lower to 0.39 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months (follow-up: 12 months; assessed with: WOMAC; Scale from: 0 to 68)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	75	76	-	MD **3.47 lower** (7.1 lower to 0.16 higher)	⨁⨁⨁◯ Moderate	CRITICAL

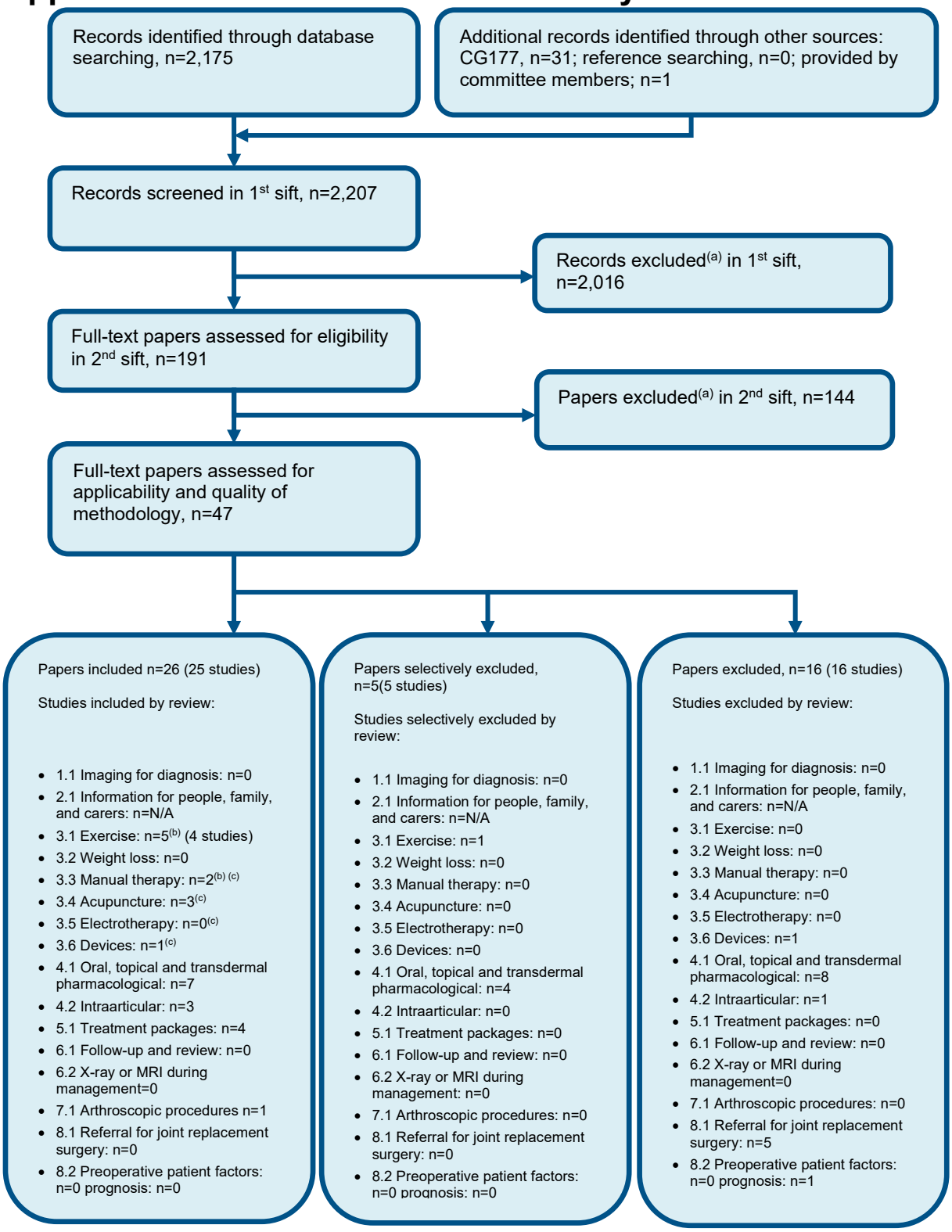
CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

Appendix G – Economic evidence study selection



(a) Non-relevant population, intervention, comparison, design or setting; non-English language.
(b) Two articles identified were applicable to Q3.1 and Q3.3, for the purposes of this diagram they have been included under Q3.1 only.
(c) One article identified was applicable to Q3.3, Q3.4, Q3.5 and Q3.6, for the purposes of this diagram it has been included under Q3.3 only.

Appendix G –Economic evidence tables

<table>
<tr><th>Study</th><th colspan="4">Abbott 2019[3] (Pinto 2013[81])</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)

Study design: Within-trial analysis (Abbott 2013[2]
Approach to analysis:
Analysis of individual level quality of life and resource use data adjusted for age, sex, primary OA joint (hip or knee), BMI, years since symptom onset, and baseline WOMAC, quadricep muscle strength, mental health, self-efficacy, and SF-6D score. Unit costs applied.
Perspective: New Zealand healthcare (public and private) and societal - only public healthcare</td>
<td>Population: People with hip or knee osteoarthritis meeting American College of Rheumatology clinical diagnostic criteria for hip or knee OA with no previous history of RA or joint replacement, no recent initiation (30 days) of opioid or corticosteroid.

Patient characteristics:
Age: 66
Male: 45%

Intervention 1:
Usual medical care (no trial physiotherapy)
Intervention 2:
Supervised exercise physiotherapy in addition to usual care*
Intervention 3:
Manual physiotherapy in addition to usual care*
Intervention 4:</td>
<td>Total costs (mean per patient):
Intervention 1: £3,577
Intervention 2: £3,550
Intervention 3: £4,602
Intervention 4: £3,744

Intervention costs only:
Intervention 1: £0
Intervention 2: £503
Intervention 3: £486
Intervention 4: £507

Currency & cost year:
2009 NZ dollars (presented here as 2009 UK pounds[(d)])]
Cost components incorporated: Medical and other healthcare consumed by participants during the trial.</td>
<td>QALYs (mean per patient):
Intervention 1: 1.31
Intervention 2: 1.46
Intervention 3: 1.39
Intervention 4: 1.38
(95% CI: NR; p=NR)</td>
<td>Full incremental analysis [(b)(c)]
<table>
<tr><th></th><th>Cost</th><th>QALYs</th><th>Inc. Cost</th><th>Inc. QALY</th><th>Cost per QALY</th></tr>
<tr><td>2</td><td>£3,550</td><td>1.46</td><td colspan="3">Baseline</td></tr>
<tr><td>1</td><td>£3,577</td><td>1.31</td><td>-£27</td><td>-0.15</td><td>D</td></tr>
<tr><td>4</td><td>£3,744</td><td>1.38</td><td>-£194</td><td>-0.07</td><td>D</td></tr>
<tr><td>3</td><td>£4,602</td><td>1.39</td><td>-£1,052</td><td>-0.08</td><td>D</td></tr>
</table>
Intervention 2 dominates all other interventions.

Probability Intervention 2 cost effective (£20K/30K threshold): NR

Analysis of uncertainty:
A sensitivity analysis was undertaken for participants with complete case data only – costs reported for this also include private healthcare costs, but intervention 2 remains dominant.
A sensitivity analysis was also undertaken excluding participants who underwent joint replacement surgery – costs reported for this also include private healthcare costs, but intervention 2 remains dominant.
Another sensitivity analysis was undertaken excluding productivity losses from the societal</td>
</tr>
</table>

perspective reported here. **Follow-up:** 2 years **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**C**ombination of exercise and manual physiotherapy in addition to usual care* *10 individual, supervised 50-minute sessions (7 sessions over a 9-week programme, with 2 booster sessions at week 16 and 54)			perspective analysis (results not informative to UK NHS context and so not reported here)
Data sources				
Health outcomes: QALYs calculated by using the time-weighted averages at the beginning and end of each measurement period. SF-12 version 2 questionnaire administered at baseline, 6 months, 1 year and 2 years. **Quality-of-life weights:** SF-6D UK tariff. **Cost sources:** Public healthcare costs - New Zealand case-mix framework for publicly funded hospitals. New Zealand Pharmaceutical Schedule, Otago District Health Board finance pricing, average fees from Dunedin metropolitan area.				
Comments				
Source of funding: Health Research Council of New Zealand and the New Zealand Lottery Grants Board. **Limitations:** 2009 New Zealand resource use and unit costs may not reflect current UK NHS practice. Within trial analysis may not reflect full body of evidence available. **Other:** None.				
Overall applicability:[e] Partially applicable **Overall quality:**[f] Potentially serious limitations				

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; D= dominated; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Intervention number in order of least to most costly (in terms of cost)

(c) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(d) Converted using 2009 purchasing power parities[78]

(e) Directly applicable / Partially applicable / Not applicable

(f) Minor limitations / Potentially serious limitations / Very serious limitations

<table>
<tr><th>Study</th><th colspan="4">Abbott 2015[1] (Pryymachenko 2021[85])</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)

Study design: 2-by-2 factorial RCT (MOA-II trial)[1]

Approach to analysis: Probabilistic model analysing individual level quality of life and resource use data adjusted for age, BMI, baseline pain intensity, duration since first diagnosis and mental health. Resource use taken from participants and unit costs applied.

Perspective: New Zealand health system

Follow-up: 2 years

Discounting: Costs: 3.5%; Outcomes: 3.5%</td>
<td>Population:
People aged 40 years or older with knee OA as defined by the American College of Rheumatology clinical criteria.

Patient characteristics:
Start age: 64
Male: 37%
Number: 75

Intervention 1:
Supervised exercise alone (twelve 45-minute individual sessions over 9 weeks) N=19
Intervention 2:
Supervised exercise with booster (twelve 45-minute individual sessions over a year) N=19
Intervention 3:
Supervised exercise plus manual therapy (two sets of twelve 45-minute individual sessions over 9 weeks) N=18</td>
<td>Total costs (mean per patient):
Intervention 1: £1,297
Intervention 2: £1,969
Intervention 3: £1,824
Intervention 4: £1,829

For incremental analyses see cost effectiveness column

Currency & cost year:
2011 NZ dollars (presented here as 2011 UK pounds[(a)])
Cost components incorporated:
Unit cost of physiotherapy, attendance during sessions, healthcare costs (both public and private)</td>
<td>QALYs (mean per patient):
Intervention 1: 1.26
Intervention 2: 1.38
Intervention 3: 1.43
Intervention 4: 1.33

For incremental analyses see cost effectiveness column</td>
<td>Full incremental analysis [(b)(c)]
<table>
<tr><th></th><th>Cost</th><th>QALYs</th><th>Inc. Cost</th><th>Inc. QALY</th><th>Cost per QALY</th></tr>
<tr><td>1</td><td>£1,297</td><td>1.26</td><td colspan="3">Baseline</td></tr>
<tr><td>3</td><td>£1,824</td><td>1.43</td><td>£527</td><td>0.17</td><td>£3,100</td></tr>
<tr><td>4</td><td>£1,829</td><td>1.33</td><td>£5</td><td>-0.10</td><td>D</td></tr>
<tr><td>2</td><td>£1,969</td><td>1.38</td><td>£145</td><td>-0.05</td><td>D</td></tr>
</table>
Probability Intervention 3 most cost effective (£20K/£30K threshold): 79%/80%[(f)]

Analysis of uncertainty: Results did not significantly alter when costs were increased by between 10% and 50%. Similarly, a decrease in QALYs by between 10% and 50% did not alter the probability of Intervention 3 being cost effective.</td>
</tr>
</table>

	Intervention 4: Supervised exercise plus manual therapy with booster sessions (two sets of twelve 45-minute individual sessions over a year) N=19			
Data sources				
Health outcomes: QALYs were calculated by using the time-weighted averages at the beginning and end of each measurement period. EQ-5D questionnaire administered at baseline, 1 year and 2 years. **Quality-of-life weights:** EQ-5D New Zealand tariff. **Cost sources:** Resource use were calculated from participant responses to the Otago Costs and Consequences Questionnaire (OCC-Q). Unit costs were taken from 2011 but the exact source is not clear.				
Comments				
Source of funding: New Zealand Lottery grants Board, New Zealand Society of Physiotherapists Scholarship Trust, Health Research Council of New Zealand and the University of Otago. **Limitations:** New Zealand healthcare system may not reflect current UK NHS. The analysis was based on a small sample size (N=75). Thirty-five patients were lost to follow-up at two years. Single-trial analysis may not reflect full body of evidence available. 2011 New Zealand resource use and unit costs may not reflect current UK NHS practice. Sources of unit costs is unclear. It is not clear what individual components make up public and private healthcare costs, and it is therefore unclear why the healthcare costs associated with Intervention 3 is substantially higher than intervention 1. **Other:** QALYs were reported to two significant figures only, though the addition of another significant figure does not significantly alter the reported cost per QALY.				
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; NZ= New Zealand; pa= probabilistic analysis; QALYs= quality-adjusted life years; RCT= randomised controlled trial

(a) Converted using 2011 purchasing power parities[78]

(b) Intervention number in order of least to most costly (in terms of cost)

(c) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost-effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(d) Directly applicable / Partially applicable / Not applicable
(e) Minor limitations / Potentially serious limitations / Very serious limitations
(f) Figures were manually read from a graph

<table>
<tr><th>Study</th><th colspan="4">MacPherson (2017[72]</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome = QALYs)

Study design: Network meta-analysis based on a systematic review of 88 trials. Three different networks were used:
1. All trials
2. Subset of trials that were graded with a low risk of bias for allocation concealment
3. Same as point 2 but further restricting trials to those that reported outcomes between 3 and 13 weeks.

Approach to analysis: QALY changes from the different networks</td>
<td>Population:
Patients reporting pain resulting from OA of the knee

Patient characteristics:
Mean age across all trials = 53-85
Male = NR

Intervention 1:
Usual care (specific treatment not described)
Intervention 2:
Static magnets
Intervention 3:
Insoles
Intervention 4:
TENS
Intervention 5:
Braces
Intervention 6:
Acupuncture
Intervention 7:
Heat treatment
Intervention 8:
Manual therapy</td>
<td>Total costs (mean per patient):
<u>All trials</u>
Intervention 1: £0
Intervention 2: £5
Intervention 3: £13
Intervention 4: £31
Intervention 5: £40
Intervention 6: £179
Intervention 7: £297
Intervention 8: £304
Intervention 9: £396
Intervention 10: £481
Intervention 11: £503
Intervention 12: £770
Intervention 13: £1,453

<u>Trials with adequate allocation concealment</u>
Intervention 1: £0
Intervention 2: £5
Intervention 3: £13
Intervention 4: £30
Intervention 5: NR
Intervention 6: £192
Intervention 7: £214</td>
<td>QALYs gained versus baseline (mean per patient):
<u>All trials</u>
Intervention 1: 0.000
Intervention 2: 0.001
Intervention 3: 0.001
Intervention 4: 0.011
Intervention 5: 0.001
Intervention 6: 0.014
Intervention 7: 0.005
Intervention 8: 0.008
Intervention 9: 0.011
Intervention 10: 0.005
Intervention 11: 0.007
Intervention 12: 0.033
Intervention 13: 0.007

<u>Trials with adequate allocation concealment</u>
Intervention 1: 0.000
Intervention 2: 0.000
Intervention 3: 0.002
Intervention 4: 0.005
Intervention 5: NR
Intervention 6: 0.017
Intervention 7: 0.003</td>
<td>Full incremental analysis[(c) (d)]:
<u>All trials</u>
<table>
<tr><th></th><th>Cost</th><th>QALYs</th><th>Inc. Cost</th><th>Inc. QALY</th><th>Cost per QALY</th><th>% most CE at £20 K</th></tr>
<tr><td>1</td><td>£0</td><td>0.000</td><td colspan="3">Baseline</td><td>0%</td></tr>
<tr><td>2</td><td>£5</td><td>0.001</td><td>£5</td><td>0.001</td><td>ED</td><td>22%</td></tr>
<tr><td>3</td><td>£13</td><td>0.001</td><td>£8</td><td>0.000</td><td>ED</td><td>0%</td></tr>
<tr><td>4</td><td>£31</td><td>0.011</td><td>£31</td><td>0.011</td><td>£2,690</td><td>49%</td></tr>
<tr><td>5</td><td>£40</td><td>0.001</td><td>£9</td><td>-0.01</td><td>D</td><td>6%</td></tr>
<tr><td>6</td><td>£179</td><td>0.014</td><td>£148</td><td>0.003</td><td>ED</td><td>6%</td></tr>
<tr><td>7</td><td>£297</td><td>0.005</td><td>£266</td><td>-0.006</td><td>D</td><td>0%</td></tr>
<tr><td>8</td><td>£304</td><td>0.008</td><td>£273</td><td>-0.003</td><td>D</td><td>0%</td></tr>
<tr><td>9</td><td>£396</td><td>0.011</td><td>£365</td><td>0.000</td><td>D</td><td>0%</td></tr>
<tr><td>10</td><td>£481</td><td>0.005</td><td>£450</td><td>-0.006</td><td>D</td><td>16%</td></tr>
<tr><td>11</td><td>£503</td><td>0.007</td><td>£472</td><td>-0.004</td><td>D</td><td>0%</td></tr>
<tr><td>12</td><td>£770</td><td>0.033</td><td>£739</td><td>0.022</td><td>£33,866</td><td>0%</td></tr>
<tr><td>13</td><td>£1,453</td><td>0.007</td><td>£683</td><td>-0.026</td><td>D</td><td>0%</td></tr>
</table>
<u>Trials with adequate allocation concealment[(e)]</u>
<table>
<tr><th></th><th>Cost</th><th>QALYs</th><th>Inc. Cost</th><th>Inc. QALY</th><th>Cost per QALY</th><th>% most CE at</th></tr>
</table>
</td>
</tr>
</table>

of analysis were combined with treatment and non-treatment-related costs.

Perspective: UK NHS

Time horizon/ treatment duration: 8 weeks

Discounting: n/a

Intervention 9: PES
Intervention 10: NMES
Intervention 11: Laser light therapy
Intervention 12: Interferential therapy
Intervention 13: PEMF

Intervention 8: £276
Intervention 9: £410
Intervention 10: NR
Intervention 11: £288
Intervention 12: £1,179
Intervention 13: £577

<u>Trials with adequate allocation concealment and an end point reported at 3-13 weeks</u>
Intervention 1: £0
Intervention 2: £5
Intervention 3: £14
Intervention 4: £30
Intervention 5: NR
Intervention 6: £192
Intervention 7: £213
Intervention 8: £277
Intervention 9: £410
Intervention 10: NR
Intervention 11: £288
Intervention 12: £1,179
Intervention 13: £277

For incremental analyses see cost effectiveness column

Currency & cost year:

Intervention 8: 0.013
Intervention 9: 0.010
Intervention 10: NR
Intervention 11: 0.003
Intervention 12: 0.016
Intervention 13: 0.008

<u>Trials with adequate allocation concealment and an end point reported at 3-13 weeks</u>

Intervention 1: 0.000
Intervention 2: -0.001
Intervention 3: 0.004
Intervention 4: 0.006
Intervention 5: NR
Intervention 6: 0.017
Intervention 7: 0.002
Intervention 8: 0.018
Intervention 9: 0.010
Intervention 10: NR
Intervention 11: 0.003
Intervention 12: 0.017
Intervention 13: 0.007

For incremental analyses see cost effectiveness column

						£20 K
1	£0	0.000	Baseline			0%
2	£5	0.000	£5	0.000	D	26%
3	£13	0.002	£13	0.002	ED	4%
4	£30	0.005	£30	0.005	£6,142	15%
6	£192	0.017	£162	0.012	£13,502	47%
7	£214	0.003	£22	-0.014	D	0%
8	£276	0.013	£84	-0.004	D	7%
11	£288	0.003	£96	-0.014	D	0%
9	£410	0.010	£218	-0.007	D	0%
13	£577	0.008	£385	-0.009	D	0%
12	£1,179	0.016	£987	-0.001	D	0%

<u>Trials with adequate allocation concealment and an end point reported at 3-13 weeks[(e)]</u>

	Cost	QALYs	Inc. Cost	Inc. QALY	Cost per QALY	% most CE at £20 K
1	£0	0.000	Baseline			0%
2	£5	-0.001	£5	-0.001	D	17%
3	£14	0.004	£14	0.004	£3,540	13%
4	£30	0.006	£16	0.002	£9,750	25%
6	£192	0.017	£162	0.011	£14,275	25%
7	£213	0.002	£21	-0.015	D	0%
8	£277	0.018	£85	0.001	£86,964	20%
13	£277	0.007	£0	-0.011	D	0%
11	£288	0.003	£11	-0.015	D	0%

		2011/12 UK pounds. **Cost components incorporated:** Physiotherapist's time to conduct weekly sessions, except for TENS, where patients self-administered after an initial physiotherapist visit. Changes in non-treatment-related visits to GPs and specialists arising from changes in EQ-5D score.		<table><tr><td>9</td><td>£410</td><td>0.010</td><td>£133</td><td>-0.008</td><td>D</td><td>0%</td></tr><tr><td>12</td><td>£1,179</td><td>0.017</td><td>£902</td><td>-0.001</td><td>D</td><td>0%</td></tr></table> **Analysis of uncertainty:** TENS was the most cost-effective alternative at a £20K threshold when a linear relationship were assumed between EQ-5D treatment effect and session duration. When all the treatment benefit were assumed in the first 20/30 minutes of the session, interferential therapy was the most cost-effective option. In an analysis of all trials, TENS remained the most cost-effective option when the duration of treatment benefit were extended by 50%.
Data sources				
Health outcomes: Study-level reported mean differences in pain as a measure of treatment effectiveness were standardised to the EQ-5D measure for each of the three network meta analyses. **Quality-of-life weights:** Generic EQ-5D quality-of-life scores were mapped from the SF-12 & SF-36 surveys, pain NRD, pain VAS and WOMAC scales. **Cost sources:** The cost to the NHS (physiotherapists time, GP and specialists' consultations) was obtained from the Personal Social Services Research Unit 2012. Equipment administered by physiotherapists (e.g., devices) were not included as the per-patient costs as these were expected to be small. **Resource use:** Estimates of resource use were based on consultations with clinical experts and published literature including trial data and NHS data. Treatment duration was based on a weighted average of the clinical trial data.				
Comments				
Source of funding: National Institute for Health Research (NIHR). **Limitations:** Unit costs taken from 2011/12 may not reflect current UK NHS practice. The time horizon was only 8 weeks. Adverse events and their downstream consequences were not considered. **Other:** Non-treatment-specific healthcare resource use was assumed to be a function of change in EQ-5D and was taken from the TOIB trial. TENS machine assumed to last for 1 year.				
Overall applicability:[(a)] Partially applicable		**Overall quality:**[(b)] Potentially serious limitations		

Abbreviations: CE= cost effective; CI = confidence interval; CUA = cost-utility analysis; D= dominated; ED= extendedly dominated; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GP= general practitioner; ICER = incremental cost-effectiveness ratio; Inc.= incremental; K= thousand; n/a = not applicable; NHS = National Health Service; NMES= neuromuscular electrical stimulation; NR = not reported; NRS = numeric rating scale; OA = Osteoarthritis; PEMF= pulsed electromagnetic field; PES= pulsed electrical stimulation; QALYs = quality-adjusted life years; SF-12 = short-form health survey 12 items; SF-36= short-form health survey 36 items; TENS= transcutaneous electrical nerve stimulation; UK= United Kingdom; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations /Potentially serious limitations / Very serious limitations

(c) Intervention number in order of least to most costly (in terms of cost)
(d) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.
(e) Interventions 5 and 10 not available because these interventions did not provide information to network meta analyses.

Appendix H – Health economic model

No original economic modelling was undertaken.

Appendix I – Excluded studies

Clinical studies

Table 15: Studies excluded from the clinical review

Study	Exclusion reason
Ahern 2018[4]	Systematic review and Meta-analysis which do not meet the PICO.
Albertin 2019[6]	Not guideline condition
Ali 2014[7]	Incorrect interventions
Alinaghizadeh 2021[8]	Insufficient treatment duration (<1 week)
Allen 2018[10]	Incorrect interventions
Alkhawajah 2019[9]	Insufficient treatment duration (<1 week)
Alper 2016[11]	Incorrect interventions. Summary of RCT (Wang 2016)
Altmis 2018	Not review population.
Anwer 2018[13]	Systematic review: methods are not adequate/unclear
Arul Pragassame 2019[14]	Incorrect comparison (a different type of exercise and manual therapy compared to exercise)
Bennell 2005[17]	Incorrect interventions. Physiotherapy included manual therapy, exercise and devices (taping), with continued exercises at home
Bennell 2014[16]	Incorrect interventions. Physical therapy included manual therapy, exercise, education and advice and devices (an optional walking stick) with continued exercises
Bennell 2015[15]	Systematic review: methods are not adequate/unclear
Bertozzi 2015[18]	Systematic review is not relevant to review question or unclear PICO. Systematic review of various interventions
Bervoets 2015[19]	Not review population. Not guideline condition
Beselga 2016[20]	Less than minimum duration
Beumer 2016[21]	Systematic review: mainly looking at exercise.
Bhagat 2020[22]	Wrong comparison (different types of manual therapy compared to each other)
Bove 2018[23]	Economic evaluation of an RCT (see Fitzgerald 2016)
Brantingham 2003[27]	Paper not available
Brantingham 2011[25]	Systematic review is not relevant to review question or unclear PICO. Not just osteoarthritis and various study types
Brantingham 2012[26]	Incorrect interventions
Brantingham 2012[24]	Systematic review is not relevant to review question or unclear PICO. Systematic review of various lower extremity conditions
Bronfort 2010[28]	Incorrect study design. Report of systematic reviews
Ceballos-laita 2019[29]	Incorrect interventions. SR on conservative treatments not just manual therapy
Chamberlain 1982[30]	Diathermy plus exercise in hospital versus exercise at home. Incorrect interventions
Cheawthamai 2014[31]	Self-administered manual therapy
Christiansen 2018[34]	Not guideline condition. Physical therapy after knee replacement
Cortes godoy 2014[35]	No scales that meet our PICO
Courtney 2016[36]	Incorrect study design
Crossley 2008[37]	Protocol for RCT
Cruz-montecinos 2016[38]	Less than minimum duration

Study	Exclusion reason
Deyle 2000[43]	No relevant outcomes
Deyle 2000[42]	Abstracts
Deyle 2005[40]	Inappropriate comparison
Deyle 2016[41]	Inappropriate comparison. Protocol for a study
Dwyer 2015[44]	Incorrect interventions
Estebanez-de-miguel 2018[45]	Inappropriate comparison. Incorrect interventions. Less than minimum duration
Fillingham 2018[46]	Inappropriate comparison.
Fish 2008[47]	Combined topical cream and knee-joint mobilisation
Fransen 2001[49]	Incorrect interventions. Combination of treatments including 20 minutes of muscle strengthening exercise or manual therapy aimed at increasing range of motion and 5-10 minutes of electrophysical agents such as heat, ultrasound, laser or interferential therapy
French 2011[50]	Systematic review is not relevant to review question or unclear PICO. Not all of our outcomes are included
French 2014	Secondary analysis of RCT
Goh 2018[53]	Protocol for a systematic review.
Gong 2019[54]	Incorrect interventions
Hart 2000[56]	Abstracts
Hinman 2007[57]	Incorrect interventions. Aquatic physical therapy
Hoeksma 2004[59]	Inappropriate comparison
Hoeksma 2005[58]	Inappropriate comparison
Iudica 2000[60]	Abstracts
Jansen 2011[61]	Systematic review focusing on exercise therapy
Jardine 2012[62]	Less than minimum duration
Jeyakumar 2017[63]	Paper not available
Kaya mutlu 2018[64]	Inappropriate comparison
Kemp 2018[65]	Incorrect interventions. Relevant to treatment package review.
Kloek 2018[66]	Inappropriate comparison
Kornkamon 2019[67]	Wrong comparison (manual therapy compared to home based exercise and education)
Li 2016[68]	Self-administered manual therapy
Li 2018[69]	Self-administered manual therapy
Lorenc 2018[70]	Not guideline condition
Lue 2017[71]	Incorrect interventions. Non-surgical interventions
Mahmooda 2020[73]	Incorrect comparison (compares two different types of manual therapy to each other)
Maicki 2017[74]	Inappropriate comparison
Nelson 2017[76]	Systematic review
Perlman 2012[80]	Inappropriate comparison
Perlman 2019[79]	Inappropriate comparison
Pinto 2013[81]	Economic evaluation of Abbott 2013
Poulsen 2011[83]	Protocol of RCT of treatment package.
Poulsen 2013[84]	Incorrect interventions. Manual therapy plus patient education so relevant to treatment packages.
Rao 2018[88]	Inappropriate comparison. Two types of mobilisation

Study	Exclusion reason
Rocchi 2017[89]	Incorrect study design. Inappropriate comparison
Romeo 2013[90]	Incorrect interventions
Salamh 2017[91]	Systematic review: study designs inappropriate
Sampath 2016[92]	Systematic review is not relevant to review question or unclear PICO. Inappropriate comparison
Scholten-peeters 2013[93]	Not guideline condition
Sit 2018[94]	Protocol for an RCT
Slawson 2014[96]	Protocol of meta-analysis of RCTs (Bennell 2014)
Sorour 2014[97]	Incorrect study design
Stein 2010[98]	Inappropriate comparison. Protocol of an RCT
Stoneman 2001[99]	Not ordered, citation only
Telci 2012[100]	Not guideline condition
Tok 2011[101]	Inappropriate comparison
Tucker 2003[102]	Inappropriate comparison, manipulation compared to medication.
Uijen 2014[103]	Non-English language studies
Villafane 2011[107]	Not patient reported outcomes
Villafane 2012[108]	Not patient reported outcomes
Villafane 2012[106]	Not patient reported outcomes
Villafane 2013[104]	Secondary analysis of RCT
Vizdoaga 2021[109]	Conference abstract
Wang 2006[111]	Non-English language studies
Wang 2015[110]	Systematic review is not relevant to review question or unclear PICO
Weleslassie 2021[112]	Systematic review; references checked (insufficient quality assessment for inclusion in this review)
Weng 2009[113]	Wrong unit of randomisation (knee)
Westad 2019[114]	Not guideline condition
Woods 2017[115]	Cost-effectiveness study from Corbett 2013 SR and Meta-analysis
Xu 2017[116]	Systematic review is not relevant to review question or unclear PICO
Zammit 2010[117]	Systematic review: study designs inappropriate

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix J – Research recommendations – full details

J.1.1 Research recommendation

What is the clinical and cost-effectiveness of manual therapy for people with osteoarthritis, when used alone and when used in combination with therapeutic exercise?

J.1.2 Why this is important

In this review, manual therapy in combination with therapeutic exercise was shown to likely be clinically and cost-effective. However, the evidence for this was based on a limited number of small trials of low quality. There was limited evidence for the clinical and cost-effectiveness of manual therapy used alone, which came from studies that were of low quality, with insufficient blinding and allocation concealment and with some imprecision. Given this, further research that was sufficiently well powered and of high quality would be important to be more certain of the benefits of manual therapy and whether it is only effective when combined with exercise or whether it is effective without exercise.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Exercise is an important part of the treatment of osteoarthritis. However, some people may find it difficult to start exercising due to initial pain. Manual therapy may be useful to initiate exercise or reduce pain so people can start exercise. Therefore, investigating the benefits of manual therapy would be useful to understand its effect for people with osteoarthritis.
Relevance to NICE guidance	The current guidance is based on small studies that were often of low quality due to risk of bias. Therefore, conducting a study with sufficient power and quality will allow for stronger recommendations to be made in the future and for the true effect of the treatment to be ascertained.
Relevance to the NHS	Manual therapy is a costly intervention requiring support from a therapist. In the current service of the NHS the potential resource impact is significant. Therefore, having up to date cost-effectiveness evidence would be important to ensure that the treatment is useful for current practice in the NHS.
National priorities	This is not an area of national priority.
Current evidence base	The current evidence for manual therapy includes short term studies for osteoarthritis of the hip, knee and hand. These generally had small numbers of participants and were of low quality due to problems with blinding and allocation concealment. Therefore, additional studies of high quality that are well powered would be important to ensuring that the true effect of the intervention can be identified.
Equality considerations	Some people may not be able to access exercise therapy and so manual therapy may be

	useful in those people (for example: people with comorbidities, people with learning disability). The committee noted that the research identified in this review does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone.

J.1.4 Modified PICO table

Population	Inclusion: Adults (age ≥16 years) with osteoarthritis affecting any joint •
Intervention	• Manual therapy alone • Manual therapy and exercise combined
Comparator	Usual care
Outcome	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [validated patient-reported outcomes, continuous data prioritised] • Minor adverse events [dichotomous] • Moderate/major adverse events [dichotomous]
Study design	Randomised control trial
Timeframe	Long term
Additional information	Adequately powered high quality randomised controlled trials. Trials with sufficient blinding, adequate randomisation methods and allocation concealment. While trials are recommended for all joint sites of osteoarthritis, trials for joints other than the hip, knee and hand are also recommended as currently no evidence exists for these.

	Subgroup analyses:
	• Presence of multimorbidity (high versus low morbidity score)
	• Age (≤/> 75 years)
	• Site of osteoarthritis
	  ○ Hip
	  ○ Knee
	  ○ Ankle
	  ○ Foot
	  ○ Toe
	  ○ Shoulder
	  ○ Elbow
	  ○ Wrist
	  ○ Hand
	  ○ Thumb
	  ○ Finger
	  ○ Temporomandibular joint (TMJ)
	  ○ Multisite
	• Remote delivery of therapy vs. delivery in person