National Institute for Health and Care Excellence

Final

Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain

[l] Evidence review for manual therapy for chronic primary pain

NICE guideline NG193

Intervention evidence review underpinning the research recommendation in the NICE guideline

April 2021

This evidence review was developed by the National Guideline Centre based at the Royal College of Physicians

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

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1 Manual therapies for chronic primary pain

1.1 Review question: What is the clinical and cost effectiveness of manual therapy for the management of chronic primary pain?

1.2 Introduction

Manual therapy is often used to treat neurological, cardio-respiratory and orthopaedic conditions, including pain. The practitioner delivering the therapy applies mechanical forces to the musculoskeletal structures, usually using the hands, in order to alter the physical and/or neurophysiological properties of the tissues.

Modern day manual therapy has been defined as: "the use of hands ……or a hands-on technique with therapeutic intent".[166] It is usually delivered as a therapeutic approach by a range of clinicians including physiotherapists, occupational therapists, osteopaths, chiropractors and massage therapists.

There are many different techniques that may be used within manual therapy, and these include:

- Soft Tissue Techniques: Mobilisation of tissues such as muscles, tendons, or ligaments, without causing movement or change of joint position for example massage, muscle energy technique, myofascial/trigger point release.
- Traction: Manual distraction of a body part, for example the neck.
- Manipulation and Mobilisation: Manual techniques specifically applied to joints. Manipulation is application of a high velocity, low amplitude force near end of range of joints. This is often, but not always, accompanied with a pop or click. Mobilisation is passive movement of joints aimed to reduce pain and/or restore range.
- Mixed Modality Manual Therapy: A combination of the above techniques.

One stated outcome of manual therapy is pain relief, however uncertainty exists regarding this outcome for people with chronic primary pain. This chapter aims to explore the effectiveness of manual therapy techniques as a treatment for the management of chronic primary pain conditions.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People, aged 16 years and over, with chronic primary pain (whose pain management is not addressed by existing NICE guidance) (chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain, chronic primary musculoskeletal pain other than orofacial) Chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) and functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms.
Interventions	• Soft tissue technique (e.g. massage, muscle energy technique, myofascial/trigger point release)

	• Traction • Manipulation/mobilisation (including spinal manipulation therapy (SMT) and Maitland technique) • Mixed modality manual therapy (soft tissue technique +/- traction +/- manipulation/mobilisation).
Comparisons	• Each other • Usual care • Acupuncture / dry needling.
Outcomes	CRITICAL: • Pain reduction (any validated scale) • Health related quality of life (including meaningful activity) • Physical function (5 minute walk, sit to stand, Roland Morris Disability Questionnaire, Oswestry Disability Index, Canadian Occupational Performance Measure) • Psychological distress (depression/anxiety) (preferably Hospital Anxiety and Depression Scale) • Pain interference (brief pain inventory interference subscale) • Pain self-efficacy (pain self-efficacy questionnaire) IMPORTANT: • Use of healthcare services • Sleep • Discontinuation. Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months.
Study design	Randomised controlled trials (RCTs) and systematic reviews of RCTs Cross-over RCTs will be considered if no non-cross-over RCT evidence is identified

1.4 Clinical evidence

1.4.1 Included studies

Fifteen studies were included in the review; [5] [34] [39] [50, 60] [103] [174] [176] [179] [215] [245] [256] [290] [20, 40, 104, 218]. These are summarised in Table 2. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10 and Table 11).

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.

1.4.2 Excluded studies

Six Cochrane reviews were identified but did not match the PICO characteristics of this review (Franco, 2016[105], Franco 2017[106], Franco 2017[107], Graham 2008[121], Gross 2015[123] and Smart 2016 [254]), due to differences in the included interventions and populations. All studies included in these Cochrane reviews were cross-checked for inclusion in this review as relevant.

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Albers 2018[5]	**Manipulation/mobilisation** (n=17). Number of sessions: 10 Duration of sessions: 45 minutes Delivered by: osteopathic practitioners Setting: single centre (Germany). Details: Large but gentle movements performed continuously and rhythmically, mobilizing dysfunctional areas of the body in a well-defined order. Slow mobilisation of the soft tissues and articular techniques are incorporated, adapted to the needs of the patient. 12 week intervention. Versus **Usual care** (n=14). Details: remained untreated during the study period	Fibromyalgia (n=50*) Mean age (SD): treatment group 55.4 (11.9), control 53.8 (16.3) years Duration of pain not reported	At 12 weeks: • Pain reduction • Quality of life • Discontinuation	*Three armed trial. Third arm (osteopathic intervention including high-velocity thrust, muscle energy technique, myofascial release, balanced ligamentous tension and visceral/cranial techniques) excluded from analysis as techniques were individually chosen according to the osteopath's findings – unclear which techniques were used.
Ariza-Mateos 2019[20]	**Mixed modality manual therapy** (n=16). Number of sessions: 2 per week for 6 weeks Duration of sessions: 45 mins Delivered by: physical therapist Setting: laboratory of the Faculty of Health Sciences, University of Granada (Spain). Details: Each session included soft tissue mobilisations and myofascial release (20min), deep-pressure massage (15min) and muscle energy techniques (10min). Durations of each were adapted to the participant's tissue response. 6 week intervention.	Chronic pelvic pain (n=49*) Mean age (SD): treatment group 40.67 (11.7), control group 42.40 (6.15) Mean years diagnosed (SD): treatment group 9.58 (5.38), control group 7.27 (5.35)	At 6 and 18 weeks: • Pain reduction • Physical function • Pain interference	* Study featured three arms, with only the latter two included here: • Graded exposure therapy plus manual therapy (n=16) • Manual therapy alone (n=16) • Control (waiting list) (n=17)

Study	Intervention and comparison	Population	Outcomes	Comments
	Versus **Usual care** (n=17). Details: waiting list control. The participants in this group also received a booklet with chronic pelvic pain information to minimize potential dropout.			
Blunt 1997[34]	**Mixed modality manual therapy** (n=10). Number of sessions: 3-5 per week. Duration of sessions: not specified. Delivered by: not specified. Setting: chiropractic and rehabilitation center (Canada). Details: soft-tissue massage, soft tissue stretching, spinal manipulation & education. 4 week intervention. Versus **Usual care** (n=11). Details: waiting list control. Following outcome assessment, also received chiropractic intervention. Both groups also received information on fibromyalgia and habits to reduce symptoms.	Fibromyalgia (n=21) Mean age (SD): treatment group 49.1 (10.1), sham group 48.78 (7.69) Mean years diagnosed (SD): treatment group 2 (1.76), sham group 3.67 (3.2)	At 4 weeks: • Pain reduction • Physical function • Discontinuation	
Brattberg 1999[39]	**Soft tissue technique** (n=27). Number of sessions: 15. Duration of sessions: not specified. Delivered by: massage therapists. Setting: not specified (Sweden). Details: program included massage of the pelvic area, back area, shoulder area, abdomen, legs and site of the pain. 10 week intervention.	Fibromyalgia (n=52) Mean age (SD): 48 (12.4) years 86% had experienced pain for >5 years and 50% for >10 years	At 10 weeks: • Pain reduction • Quality of life • Physical function • Psychological distress • Sleep • Discontinuation	

Study	Intervention and comparison	Population	Outcomes	Comments
	Versus **Usual care (n=25).** Details: received no treatment, but took part in group discussions for the last 5 weeks of the treatment period.			
Campa-Moran 2015[50]	**Acupuncture/dry needling** (n=12). Number of sessions: 2. Duration of sessions: not specified. Delivered by: not specified. Setting: not specified (Spain). Details: this group received two treatments of bilateral dry needling on levator scapulae and upper trapezius muscles and a passive stretching technique. 2 day intervention **Soft tissue technique** (n=12). Number of sessions: 2. Duration of sessions: not specified. Delivered by: not specified. Setting: not specified (Spain). Details: patients received a bilateral osteopathic manual therapy treatment based on the ischemic compression technique over both the levator scapulae and upper trapezius muscles, as well as a dynamic soft tissue mobilisation (DSTM) on the upper trapezius. 2 day intervention. **Manipulation/mobilization** (n=12). Number of sessions: 2. Duration of sessions: not specified. Delivered by: not specified. Setting: not specified (Spain).	Chronic orofacial pain (n=36) Mean age (SD): dry needling group 53.9 (12.7), soft tissue group 45.8 (15.4), mobilisation group 48.7 (10.2). Mean pain duration (SD): dry needling 10 (2.9), soft tissue 11.8 (4.4), mobilisation 14 (3.6) months	At 9 days: • Pain reduction • Physical function • Psychological distress	

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: this group received an osteopathic manual therapy protocol with a neural/joint approach, with three techniques: (1) anterior-posterior upper cervical mobilisation with wedge; (2) the cervical lateral glide mobilisation technique at C4 and C5; and (3) neural thoracic mobilisation with wedge. 2 day intervention.			
Ceca 2017[60]	**Soft tissue technique** (n=33). Number of sessions: 2 per week. Duration of sessions: 50 minutes. Delivered by: sessions led by specialist in physical activity. Setting: sports centres (Spain). Details: self-myofascial release program featuring mobility exercises, self-myofascial release exercises (applying pressure with objects such as balls and rollers) and static stretching. 20 week intervention. Versus **Usual care** (n=33). Details: the control group received no treatment.	Fibromyalgia (n=66) Mean age (SD): not stated. Duration of pain not reported	At 20 weeks: • Quality of life • Discontinuation	
FitzGerald 2012[104]	**Soft tissue technique** (n=42). Number of sessions: up to 10 sessions over 12 weeks Duration of sessions: 60 mins Delivered by: physical therapist Setting: 11 clinical centres (USA) Details: Global therapeutic massage (GTM). Followed a traditional full-body Western massage programme. 12 week intervention.	Interstitial cystitis/painful bladder syndrome (IC/PBS) (n=81) Mean age (SD): soft tissue technique group 43 (12.9), mobilisation/manipulation group 43.1 (15.1) All participants had a clinical diagnosis of IC/PBS for at	At 12 weeks: • Pain reduction • Quality of life • Discontinuation	

Study	Intervention and comparison	Population	Outcomes	Comments
	Versus **Manipulation/mobilization** (n=39). Number of sessions: up to 10 sessions over 12 weeks Duration of sessions: 60 mins Delivered by: physical therapist Setting: 11 clinical centres (USA) Details: Myofascial physical therapy (MPT). Participants received targeted internal and external tissue manipulation focusing on the muscles and connective tissue of the pelvic floor, hip girdle, and abdomen. 12 week intervention.	least 3 months but no more than 3 years.		
Lin 2013[174]	**Mixed modality manual therapy** (n=33). Number of sessions: 8. Duration of sessions: 20 minutes. Delivered by: therapist who had at least 5 years' experience practicing Long's manipulation for neck pain. Setting: not specified (China). Details: Long's manipulation delivered in 4 steps: 1) relaxation; 2) manipulation; 3) provocative massage; 4) gentle massage. 24 day intervention Versus **Soft tissue technique** (n=30). Number of sessions: 8. Duration of sessions: 20 minutes. Delivered by: therapist who had at least 5 years' experience practicing Long's manipulation for neck pain. Setting: not specified (China).	Chronic neck pain (n=63) Mean age (SD): manipulation group 38.94 (11.71), massage group 40.90 (11.80). Mean duration of pain (SD): manipulation 37.06 (35.2), soft tissue group 39.23 (28.73) months	At 24 days and 4 months: • Pain reduction • Discontinuation	Inclusion criteria: a diagnosis of mechanical neck pain, more than three month history of neck pain, age between eighteen and sixty-five and being able to read Chinese. Neck pain referred from peripheral joints or viscera, rheumatic fibromyalgia and neurasthenia were excluded. Patients with a history of whiplash or surgery to the neck, diagnosis of cervical radiculopathy or myelopathy were also excluded.

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: patients in the control group received only the traditional Chinese massage techniques from the Long's manipulation program. 24 day intervention.			
Llamas-Ramos 2014[176]	**Soft tissue technique** (n=47). Number of sessions: 2. Duration of sessions: not specified. Delivered by: clinical therapist. Setting: not specified (Spain). Details: trigger point manual therapy. Pressure was applied over the upper trapezius trigger point with progressively increasing pressure, followed by stretching of the taut-band muscle fibres and passive stretching of the upper trapezius muscle (45 seconds). 2 week intervention Versus **Acupuncture/dry needling** (n=47). Number of sessions: 2. Duration of sessions: not specified. Delivered by: clinical therapist. Setting: not specified (Spain). Details: trigger point dry needling was applied to the upper trapezius using the fast-in and fast-out technique. 2 week intervention.	Chronic neck pain (n=94) Mean age (SD): manual therapy group 31 (2), dry needling group 31 (3). Duration of pain in months (SD): manual therapy group 7.1 (2.9), dry needling group 7.4 (2.6)	At 4 weeks: • Pain reduction • Discontinuation	Mechanical neck pain was defined as neck and shoulder pain with symptoms provoked by neck postures, neck movement or palpation of the cervical muscles. Participants were examined for the presence of active trigger points in the upper trapezius muscle by a clinician with more than 6 years of experience in the management of trigger points.
Madson 2010[179]	**Manipulation/mobilization** (n=11). Number of sessions: 2 or 3 per week (depending on ability to attend). Duration of sessions: 30 minutes. Delivered by: physical therapist. Setting: physical therapy practice of a tertiary care centre (USA).	Chronic neck pain (n=23) Mean age (SD): mobilisation group 52.2 (14), massage group 47.3 (15.3).	At 4 weeks: • Pain reduction • Physical function • Discontinuation	Stratification: Because symptoms of cervical spine osteoarthritis have been reported to be more prominent after the age of 60, subjects were stratified by age (</=60, >60 years) before

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: subjects received joint mobilisation to the cervical spine, including transverse glides posterior/anterior glides and rotational techniques. 4 week intervention. Versus **Soft tissue technique** (n=12). Number of sessions: 2 or 3 per week (depending on ability to attend). Duration of sessions: 30 minutes. Delivered by: physical therapist. Setting: physical therapy practice of a tertiary care centre (USA). Details: Subjects received sedative massage to the neck and upper back, including effleurage, stroking and petrissage. 4 week intervention All subjects received most heat packs to their neck and upper back for 20 to 30 minutes before treatment. In addition, all subjects received postural education and were taught range of motion exercises.	All subjects had neck pain of at least 12 weeks duration.		randomization to ensure a balanced distribution.
Plews-Ogan 2005 [215]	**Soft tissue technique** (n=10). Number of sessions: 1 per week. Duration of sessions: 1 hour. Delivered by: 3 licensed massage therapists. Setting: not specified (USA). Details: patients received massage sessions. The techniques used were at the discretion of the therapists and included Swedish, deep-tissue, neuromuscular and pressure-point techniques. 8 week intervention	Chronic musculoskeletal pain (n=20) Mean age: 46.5 years Duration of pain not reported	At 8 weeks: • Pain reduction • Quality of life	Study published limited information about its population, only defined as “adults with musculoskeletal pain for greater than 3 months.” Exclusion criteria: prisoner status, cognitive impairment, lack of reliable

Study	Intervention and comparison	Population	Outcomes	Comments
	Versus **Usual care** (n=10). Details: standard care at the two practices was to be seen by a primary care physician at least every 3 months with medication adjustments made as indicated.			transportation, or being pregnant. Note: pilot study to determine feasibility. Limited results published. Three armed study – third arm (MBSR) excluded
Puntumetakul 2019[218]	**Mixed modality manual therapy** (n=15). Number of sessions: 6 sessions over 3 weeks Duration of sessions: not specified. Delivered by: not specified. Setting: not specified (Thailand). Details: Participants received thoracic manipulation (as described below) followed by the Rungthip massage technique (the participant laid on their side while the therapist pressed a thumb along treatment lines from the scapula to the lowest rib). 3 week intervention. Versus **Manipulation/mobilization** (n=15). Number of sessions: 6 sessions over 3 weeks Duration of sessions: not specified. Delivered by: not specified. Setting: not specified (Thailand). Details: Thoracic manipulation was performed directly on both sides of the T6-T7 zygapophyseal joints. 3 week intervention.	Mechanical neck pain (n=30) Mean age (SD): mixed manual therapy group 23.07 (2.71), manipulation/mobilisation group 23.27 (4.5) All participants had a mechanical neck pain for a duration of at least 3 months.	At 3 weeks: • Pain reduction	

Study	Intervention and comparison	Population	Outcomes	Comments
	Participants in both groups also received neck care education, including advice on how to adopt a neutral sitting posture and safe lifting posture.			
Sherman 2014[245]	**Soft tissue technique** (n=38). Number of sessions: 1 per week. Duration of sessions: 1 hour. Versus **Soft tissue technique** (n=38). Number of sessions: 2 per week. Duration of sessions: 30 minutes. Versus **Soft tissue technique** (n=39). Number of sessions: 2 per week. Duration of sessions: 1 hour. Versus **Soft tissue technique** (n=37). Number of sessions: 3 per week. Duration of sessions: 30 minutes. Versus **Soft tissue technique** (n=39). Number of sessions: 3 per week. Duration of sessions: 1 hour.	Chronic nonspecific neck pain (n=228) Mean age (SD): control 44.4 (12.2), 1x60min/week 50.2 (10.9), 2x30min/week 42.3 (11.3), 2x60min/week 48.7 (11.5), 3x30min/week 45.7 (11.5), 3x60min/week 49 (9.9) years. Majority of participants had pain >3 years	At 5 weeks: • Pain reduction • Physical function • Psychological distress	6 armed trial – 5 massage dosing schedules pooled for analysis and compared against waiting list control Individuals whose neck pain had a pathologically identifiable cause were excluded

Study	Intervention and comparison	Population	Outcomes	Comments
	Delivered by: licensed therapists with at least 5 years of experience Setting: research clinic Details: included range of motion assessment, hands-on check-in, massage applied directly to the neck, addressing compensatory patterns, and integration (reestablishment within a patient of being in a unified body after having received intensive isolated work). 4 weeks intervention. **Usual care** (n=37) Details: waiting list			
Sobhani 2017[256]	**Mixed modality manual therapy** (n=13). Number of sessions: 5. Duration of sessions: not specified. Delivered by: physical therapist. Setting: not specified (Iran). Details: subjects received bilateral manual therapy based on ischemic compression technique over the levator scapulae and upper trapezius muscles, dynamic soft tissue mobilisation on the upper trapezius, anterior-posterior mobilisation of the upper thoracic spine, cervical lateral glide mobilisation and neural thoracic mobilisation. 10 day intervention. Versus **Acupuncture/dry needling** (n=13). Number of sessions: 5. Duration of sessions: not specified. Delivered by: physical therapist. Setting: not specified (Iran).	Chronic orofacial pain (n=39*) Mean age (SD): manual therapy group 35.9 (11.4), dry needling group 34.6 (10.5). Duration of symptoms in months (SD): manual therapy group 15.1 (7.5), dry needling group 12.6 (4.4)	At 10 days: • Pain reduction • Physical function • Psychological distress	*Three arm trial. Third arm (kinesio taping) excluded from this analysis as it is not relevant to this review protocol. Cervical pain was explained as mechanical pain in cervical region muscles that can be aggravated with sustained posture and different cervical motions. Minimum pain for inclusion was 2 out of 10 on a visual analogue scale (VAS).

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: subjects received bilateral dry needling for the upper trapezius and levator scapulae muscles followed by passive stretching. 10 day intervention.			
Zaproudina 2007 [290]	**Soft tissue technique** (n=35). Number of sessions: 5. Duration of sessions: 1 hour. Delivered by: registered therapists. Setting: not specified (Finland). Details: patients received upper body massage. 5-10 week intervention. Versus **Manipulation/mobilization** (n=35). Number of sessions: 5. Duration of sessions: 1.5 hours. Delivered by: experienced Finnish bone setters. Setting: not specified (Finland). Details: patients received traditional bone setting. 5-10 week intervention.	Chronic neck pain (n=105*) Mean age (SD): mobilisation group 41.2 (5.7), massage group 42.4 (5.9). Neck pain duration in years (SD): mobilisation group 11.7 (6.2), massage group 11.2 (7.3)	At 1 month post intervention: • Pain reduction • Physical function • Discontinuation	*Three arm trial. Third arm (traditional physiotherapy) excluded from this analysis as it is not relevant to this review protocol. Chronic non-specific neck pain was defined as a clinical diagnosis of "tension neck" without radicular arm symptoms, with a minimum 3 out of 10 on VAS pain scale. No other diagnosis criteria were reported.

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: mixed modality manual therapy vs. usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Mixed modality manual therapy (95% CI)
Pain reduction at ≤3 months (BPI; VAS 0-10, final values and change scores) Scale from: 0 to 10.	52 (2 studies) 4-6 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain reduction at ≤3 months (bpi; vas 0-10, final values and change scores) in the control groups was 4.63	The mean pain reduction at ≤3 months (bpi; vas 0-10, final values and change scores) in the intervention groups was 0.96 lower (2.89 lower to 0.97 higher)
Pain reduction at >3 months (BPI, 0-10, final scores, high scores are poor outcome) Scale from: 0 to 10.	33 (1 study) 18 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain reduction at >3 months (bpi, 0-10, final scores, high scores are poor outcome) in the control groups was 6	The mean pain reduction at >3 months (bpi, 0-10, final scores, high scores are poor outcome) in the intervention groups was 1.92 lower (2.98 to 0.86 lower)
Physical function at ≤3 months (Oswestry Disability Index, 0-100, change scores and final scores, high is poor outcome) Scale from: 0 to 100.	52 (2 studies) 4-6 weeks	⊕⊖⊖⊖ VERY LOW2 due to risk of bias, imprecision		The mean physical function at ≤3 months (Oswestry disability index, 0-100, change scores and final scores, high is poor outcome) in the control groups was 33.33	The mean physical function at ≤3 months (Oswestry disability index, 0-100, change scores and final scores, high is poor outcome) in the intervention groups was 8.3 lower (15.46 to 1.14 lower)
Physical function at >3 months (Oswestry Disability Index, 0-100, final scores, high is poor outcome) Scale from: 0 to 100.	33 (1 study) 18 weeks	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean physical function at >3 months (Oswestry disability index, 0-100, final scores, high is poor outcome) in the control groups was 28.7	The mean physical function at >3 months (Oswestry disability index, 0-100, final scores, high is poor outcome) in the intervention groups was 16.78 lower (23.31 to 10.25 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Mixed modality manual therapy (95% CI)
Pain interference at ≤3 months (BPI – interference, 0-10, final scores, high is poor outcome) Scale from: 0-10.	33 (1 study) 6 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain interference at ≤3 months (bpi – interference, 0-10, final scores, high is poor outcome) in the control groups was 4.5	The mean pain interference at ≤3 months (bpi – interference, 0-10, final scores, high is poor outcome) in the intervention groups was 0.13 lower (1.7 lower to 1.44 higher)
Pain interference at >3 months (BPI – interference, 0-10, final scores, high is poor outcome) Scale from: 0-10.	33 (1 study) 18 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain interference at >3 months (bpi – interference, 0-10, final scores, high is poor outcome) in the control groups was 5.73	The mean pain interference at >3 months (bpi – interference, 0-10, final scores, high is poor outcome) in the intervention groups was 0.64 higher (0.15 lower to 1.43 higher)
Discontinuation at ≤3 months	21 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.22 (0.01 to 4.06)	Moderate	
				182 per 1000	142 fewer per 1000 (from 180 fewer to 557 more)

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

Table 4: Clinical evidence summary: soft tissue technique vs. usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Soft tissue technique (95% CI)
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome,	286 (3 studies) 5-10 weeks	⨁⨁⊖⊖ LOW1,2,3 due to risk of		The mean pain reduction at ≤3 months (pain on VASs, 0-100, high is poor outcome, final	The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values and

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Soft tissue technique (95% CI)
final values and change scores) Scale from: 0 to 100.		bias, imprecision		values and change scores) in the control groups was 64.62	change scores) in the intervention groups was 11.83 lower (18.53 to 5.13 lower)
Health related quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	48 (1 study) 10 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean health related quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final score) in the control groups was 64.86	The mean health related quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final score) in the intervention groups was 12.77 lower (21.93 to 3.61 lower)
Health related quality of life at ≤3 months (SF-12 Mental health, 0-100, high is good outcome, change score) Scale from: 0 to 100.	17 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision		The mean health related quality of life at ≤3 months (sf-12 mental health, 0-100, high is good outcome, change score) in the control groups was 3.9	The mean health related quality of life at ≤3 months (sf-12 mental health, 0-100, high is good outcome, change score) in the intervention groups was 9.7 higher (10.56 lower to 29.96 higher)
Health related quality of life at >3 months (FIQ, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	43 (1 study) 20 weeks	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision		The mean health related quality of life at >3 months (FIQ, 0-100, high is poor outcome, final score) in the control groups was 35.22	The mean health related quality of life at >3 months (FIQ, 0-100, high is poor outcome, final score) in the intervention groups was 6.23 lower (11.78 to 0.68 lower)
Physical function at ≤3 months (Disability Rating Index, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	48 (1 study) 10 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical function at ≤3 months (disability rating index, 0-100, high is poor outcome, final score) in the control groups was 64	The mean physical function at ≤3 months (disability rating index, 0-100, high is poor outcome, final score) in the intervention groups was 7.17 lower (17.07 lower to 2.73 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Soft tissue technique (95% CI)
Physical function at ≤3 months (Neck Disability Index, 0-50, high is poor outcome, change scores) Scale from: 0 to 50.	221 (1 study) 5 weeks	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision		The mean physical function at ≤3 months (neck disability index, 0-50, high is poor outcome, change scores) in the control groups was 1.45	The mean physical function at ≤3 months (neck disability index, 0-50, high is poor outcome, change scores) in the intervention groups was 3.11 lower (4.9 to 1.32 lower)
Psychological distress at ≤3 months (HADS depression subscale, 0-21, high is poor outcome, final score) Scale from: 0 to 21.	48 (1 study) 10 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological distress at ≤3 months (HADS depression subscale, 0-21, high is poor outcome, final score) in the control groups was 8.64	The mean psychological distress at ≤3 months (HADS depression subscale, 0-21, high is poor outcome, final score) in the intervention groups was 2.4 lower (4.87 lower to 0.07 higher)
Psychological distress at ≤3 months (HADS anxiety subscale, 0-21, high is poor outcome, final score) Scale from: 0 to 21.	48 (1 study) 10 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological distress at ≤3 months (HADS anxiety subscale, 0-21, high is poor outcome, final score) in the control groups was 9.08	The mean psychological distress at ≤3 months (HADS anxiety subscale, 0-21, high is poor outcome, final score) in the intervention groups was 1.82 lower (4.23 lower to 0.59 higher)
Psychological distress at ≤3 months (Perceived Stress Scale, 0-40, high is poor outcome, change scores) Scale from: 0 to 40.	227 (1 study) 5 weeks	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision		The mean psychological distress at ≤3 months (perceived stress scale, 0-40, high is poor outcome, change scores) in the control groups was -0.42	The mean psychological distress at ≤3 months (perceived stress scale, 0-40, high is poor outcome, change scores) in the intervention groups was 1.45 lower (3.58 lower to 0.69 higher)
Sleep disturbance at ≤3 months (mean value for 10 questions about sleep, 0-5, high is poor outcome, final	48 (1 study) 10 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of		The mean sleep disturbance at ≤3 months (mean value for 10 questions about sleep, 0-5, high is poor outcome, final	The mean sleep disturbance at ≤3 months (mean value for 10 questions about sleep, 0-5, high is poor outcome, final score) in the

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Soft tissue technique (95% CI)
score) Scale from: 0 to 5.		bias, indirectness, imprecision		score) in the control groups was 3.62	intervention groups was 0.35 lower (0.75 lower to 0.05 higher)
Discontinuation at ≤3 months	52 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 2.78 (0.31 to 24.99)	Moderate	
				80 per 1000	142 more per 1000 (from 55 fewer to 1000 more)
Discontinuation at >3 months	66 (1 study) 20 weeks	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RD 0 (-0.06 to 0.06)	Moderate	
				0 per 1000	0 more per 1000 (from 60 fewer to 60 more)

1 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
2 Indirectness in comparator for Brattberg 1999: half of the usual care control group received different care (group discussions once per week).
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 5: Clinical evidence summary: manipulation/mobilisation vs. usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Manipulation/mobilisation (95% CI)
Pain reduction at ≤3 months (final values) VAS 0-10. Scale from: 0 to 10.	30 (1 study) 12 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain reduction at ≤3 months (final values) in the control groups was 6.6	The mean pain reduction at ≤3 months (final values) in the intervention groups was 2.3 lower (3.8 to 0.8 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Manipulation/mobilisation (95% CI)
Quality of life at ≤3 months (final values) FIQ . Scale from: 0 to 100.	30 (1 study) 12 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean quality of life at ≤3 months (final values) in the control groups was 51.8	The mean quality of life at ≤3 months (final values) in the intervention groups was 11.7 lower (25.15 lower to 1.75 higher)
Discontinuation	31 (1 study) 12 weeks	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 6.19 (0.12 to 317.97)	0 per 1000	58 more per 1000 (from 97 fewer to 215 more)

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

Table 6: Clinical evidence summary: mixed modality manual therapy vs. soft tissue technique

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Soft tissue technique	Risk difference with Mixed modality manual therapy (95% CI)
Pain reduction at ≤3 months (NRS, 0-10, high is poor outcome, final score) Scale from: 0 to 10.	63 (1 study) 24 days	⨁⨁⨁⨀ MODERATE 1 due to risk of bias		The mean pain reduction at ≤3 months (NRS, 0-10, high is poor outcome, final score) in the control groups was 4.04	The mean pain reduction at ≤3 months (NRS, 0-10, high is poor outcome, final score) in the intervention groups was 1.98 lower (2.78 to 1.18 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Soft tissue technique	Risk difference with Mixed modality manual therapy (95% CI)
Pain reduction at >3 months (NRS, 0-10, high is poor outcome, final score) Scale from: 0 to 10.	63 (1 study) 4 months	⨁⨁⨀⨀ LOW1 due to risk of bias		The mean pain reduction at >3 months (NRS, 0-10, high is poor outcome, final score) in the control groups was 4.54	The mean pain reduction at >3 months (NRS, 0-10, high is poor outcome, final score) in the intervention groups was 2.47 lower (3.42 to 1.52 lower)
Discontinuation at ≤3 months	63 (1 study) 24 days	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.45 (0.09 to 2.31)	Moderate	
				133 per 1000	73 fewer per 1000 (from 121 fewer to 174 more)

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

Table 7: Clinical evidence summary: mixed modality manual therapy vs. manipulation/mobilisation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Manipulation/mobilisation	Risk difference with Mixed modality manual therapy (95% CI)
Pain reduction at ≤3 months (pain at rest on VAS, 0-100, final scores, high is poor outcome) Scale from: 0 to 100.	30 (1 study) 3 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean pain reduction at ≤3 months (pain at rest on VAS, 0-100, final scores, high is poor outcome) in the control groups was 20.71	The mean pain reduction at ≤3 months (pain at rest on VAS, 0-100, final scores, high is poor outcome) in the intervention groups was 11.04 lower (18.12 to 3.96 lower)

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

Table 8: Clinical evidence summary: manipulation/mobilisation vs. soft tissue technique

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Soft tissue technique	Risk difference with Manipulation/mobilisation (95% CI)
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values and change scores) Scale from: 0 to 100.	125 (3 studies) 9-84 days	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values and change scores) in the control groups was 32.7	The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values and change scores) in the intervention groups was 11.53 lower (24.86 lower to 1.8 higher)
Pain reduction at >3 months (pain reduction on VAS, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	68 (1 study)	⨁⨁⊖⊖ LOW1,3 due to risk of bias, imprecision		The mean pain reduction at >3 months (pain reduction on VAS, 0-100, high is poor outcome, final score) in the control groups was 25.4	The mean pain reduction at >3 months (pain reduction on VAS, 0-100, high is poor outcome, final score) in the intervention groups was 7.5 lower (17.09 lower to 2.09 higher)
Health related quality of life at ≤3 months (SF-12 Physical component, 0-100, high is good outcome, final values and change scores) Scale from: 0 to 100.	78 (1 study) 12 weeks	⨁⨁⊖⊖ LOW1 due to risk of bias		The mean health related quality of life at ≤3 months (sf-12 physical component, 0-100, high is good outcome, final values and change scores) in the control groups was 46	The mean health related quality of life at ≤3 months (sf-12 physical component, 0-100, high is good outcome, final values and change scores) in the intervention groups was 0.4 lower (4.82 lower to 4.02 higher)
Health related quality of life at ≤3 months (SF-12 Mental component, 0-100, high is good outcome, final values and change scores) Scale from: 0 to 100.	78 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision		The mean health related quality of life at ≤3 months (sf-12 mental component, 0-100, high is good outcome, final values and change scores) in the control groups was 49.3	The mean health related quality of life at ≤3 months (sf-12 mental component, 0-100, high is good outcome, final values and change scores) in the intervention groups was 4.3 lower (8.63 lower to 0.03 higher)
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values)	48 (2 studies) 9-28 days	⨁⊖⊖⊖ VERY LOW1,3		The mean physical function at ≤3 months (neck disability index, 0-100, high is poor	The mean physical function at ≤3 months (neck disability index, 0-100, high is poor outcome, final values) in

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Soft tissue technique	Risk difference with Manipulation/mobilisation (95% CI)
		due to risk of bias, imprecision		outcome, final values) in the control groups was 12.88	the intervention groups was 5.11 lower (8.88 to 1.35 lower)
Physical function at >3 months (Neck Disability Index, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	68 (1 study)	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision		The mean physical function at >3 months (neck disability index, 0-100, high is poor outcome, final score) in the control groups was 15.3	The mean physical function at >3 months (neck disability index, 0-100, high is poor outcome, final score) in the intervention groups was 3.6 lower (8.13 lower to 0.93 higher)
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values)	24 (1 study)	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean psychological distress at ≤3 months (pain catastrophizing scale, 0-52, high is poor outcome, final values) in the control groups was 16.4	The mean psychological distress at ≤3 months (pain catastrophizing scale, 0-52, high is poor outcome, final values) in the intervention groups was 3.3 lower (7.01 lower to 0.41 higher)
Discontinuation at ≤3 months	104 (2 studies) 4-12 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RD -0.02	Moderate	
				42 per 1000	43 fewer per 1000 (from 39 fewer to 46 fewer)
Discontinuation at >3 months	70 (1 study)	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	OR 0.13 (0.01 to 2.14)	Moderate	
				57 per 1000	49 fewer per 1000 (from 56 fewer to 58 more)

1 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
2 Heterogeneity, I^2>50%, p=0.05, unexplained by subgroup analysis.
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 9: Clinical evidence summary: mixed modality manual therapy vs. acupuncture/dry needling

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Acupuncture/dry needling	Risk difference with Mixed modality manual therapy (95% CI)
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	26 (1 study) 10 days	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final score) in the control groups was 39.2	The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final score) in the intervention groups was 5.4 lower (18.3 lower to 7.5 higher)
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	26 (1 study) 10 days	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean physical function at ≤3 months (neck disability index, 0-100, high is poor outcome, final score) in the control groups was 16.7	The mean physical function at ≤3 months (neck disability index, 0-100, high is poor outcome, final score) in the intervention groups was 2.9 higher (1.22 lower to 7.02 higher)
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) Scale from: 0 to 52.	26 (1 study) 10 days	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological distress at ≤3 months (pain catastrophizing scale, 0-52, high is poor outcome, final values) in the control groups was 15.2	The mean psychological distress at ≤3 months (pain catastrophizing scale, 0-52, high is poor outcome, final values) in the intervention groups was 1.8 higher (2.71 lower to 6.31 higher)

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

Table 10: Clinical evidence summary: soft tissue technique vs. acupuncture/dry needling

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Acupuncture/dry needling	Risk difference with Soft tissue technique (95% CI)
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) Scale from: 0 to 100.	115 (2 studies) 9-28 days	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) in the control groups was 11.15	The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) in the intervention groups was 10.19 higher (9.35 lower to 29.73 higher)
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values) Scale from: 0 to 100.	24 (1 study) 9 days	⨁⨁⊖⊖ LOW1,3 due to risk of bias, imprecision		The mean physical function at ≤3 months (neck disability index, 0-100, high is poor outcome, final values) in the control groups was 12.2	The mean physical function at ≤3 months (neck disability index, 0-100, high is poor outcome, final values) in the intervention groups was 3 higher (1.35 lower to 7.35 higher)
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) Scale from: 0 to 52.	24 (1 study) 9 days	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision		The mean psychological distress at ≤3 months (pain catastrophizing scale, 0-52, high is poor outcome, final values) in the control groups was 18.2	The mean psychological distress at ≤3 months (pain catastrophizing scale, 0-52, high is poor outcome, final values) in the intervention groups was 1.8 lower (4.42 lower to 0.82 higher)
Discontinuation at ≤3 months	94 (1 study) 2 weeks	⨁⨁⨁⊖ MODERATE1, 3 due to risk of bias	RD 0 (-0.04 to 0.04)	Moderate	
				0 per 1000	0 more per 1000 (from 40 fewer to 40 more)

1 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
2 Heterogeneity, I^2=50%, p=0.04, unexplained by subgroup analysis
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 11: Clinical evidence summary: manipulation/mobilisation vs. acupuncture/dry needling

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Acupuncture/dry needling	Risk difference with Manipulation/mobilisation (95% CI)
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) Scale from: 0 to 100.	24 (1 study) 9 days	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) in the control groups was 13.3	The mean pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) in the intervention groups was 3.9 lower (15.73 lower to 7.93 higher)
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values) Scale from: 0 to 100.	24 (1 study) 9 days	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean physical function at ≤3 months (neck disability index, 0-100, high is poor outcome, final values) in the control groups was 12.2	The mean physical function at ≤3 months (neck disability index, 0-100, high is poor outcome, final values) in the intervention groups was 2.2 lower (6.55 lower to 2.15 higher)
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) Scale from: 0 to 52.	24 (1 study) 9 days	⨁⨁⨁⊖ MODERATE1 due to risk of bias		The mean psychological distress at ≤3 months (pain catastrophizing scale, 0-52, high is poor outcome, final values) in the control groups was 18.2	The mean psychological distress at ≤3 months (pain catastrophizing scale, 0-52, high is poor outcome, final values) in the intervention groups was 5.1 lower (7.81 to 2.39 lower)

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

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were included.

1.5.2 Excluded studies

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

See also the health economic study selection flow chart in appendix G.

1.5.3 Unit costs

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

Table 12: UK costs of healthcare professionals

Healthcare professional	Cost (per hour)
Community physiotherapist (band 5/6/7)	£52 / £64 / £78

Source: PSSRU 2018[75]

Note: These costs include the ratio of direct to indirect time with patients of 1.37 from the PSSRU. And qualification costs.

1.6 Evidence statements

1.6.1 Clinical evidence statements

Mixed modality manual therapy versus usual care/acupuncture/dry needling

Pain reduction

Low quality evidence from 2 studies with a total of 52 participants showed no clinically important difference between mixed modality manual therapy and usual care at time points up to 3 months. Low quality evidence from 1 study with a total of 33 participants showed a clinically important benefit of mixed modality manual therapy over usual care at time points after 3 months. Low quality evidence from 1 study with a total of 26 participants showed no clinically important difference between mixed modality manual therapy and acupuncture/dry needling at time points up to 3 months.

Physical function

Very low quality evidence from 2 studies with a total of 52 participants showed a clinically important benefit of mixed modality manual therapy over usual care at time points up to 3 months. Low quality evidence from 1 study with a total of 33 participants showed a clinically important benefit of mixed modality manual therapy over usual care at time points after 3 months. Low quality evidence from 1 study with a total of 26 participants showed a clinically important benefit of acupuncture/dry needling over mixed modality manual therapy at time points up to 3 months.

Psychological distress

Very low quality evidence from 1 study with a total of 26 participants showed no clinically important difference between mixed modality manual therapy and acupuncture/dry needling at time points up to 3 months.

Pain interference

Very low quality evidence from 1 study with a total of 33 participants showed no clinically important difference between mixed modality manual therapy and usual care at time points up to or after 3 months.

Discontinuation

Very low quality evidence from 1 study with a total of 21 participants showed fewer trial discontinuations from the mixed modality manual therapy arm than from usual care.

Soft tissue technique versus usual care/acupuncture/dry needling

Pain reduction

Low quality evidence from 3 studies with a total of 286 participants showed a clinically important benefit of soft tissue technique over usual care at time points up to 3 months. Very low quality evidence from 2 studies with a total of 115 participants showed a clinically important benefit of acupuncture/dry needling over soft tissue technique at time points up to 3 months.

Quality of life

Very low quality evidence from 1 study with a total of 48 participants showed a clinically important benefit of soft tissue technique over usual care at time points up to 3 months, but very low quality evidence from 1 study with a total of 17 participants showed no clinically important difference between soft tissue technique and usual care. Very low quality evidence from 1 study with a total of 43 participants showed a clinically important benefit of soft tissue technique over usual care at time points after 3 months.

Physical function

Low quality evidence from 1 study with a total of 221 participants showed a clinically important benefit of soft tissue technique over usual care at time points up to 3 months, but very low quality evidence from 1 study with a total of 48 participants showed no clinically important difference between soft tissue technique and usual care. Low quality evidence from 1 study with a total of 24 participants showed a clinically important benefit of acupuncture/dry needling over soft tissue technique at time points up to 3 months.

Psychological distress

Very low quality evidence from 1 study with a total of 48 participants showed a clinically important benefit of soft tissue technique over usual care at time points up to 3 months, but low to very low quality evidence from 2 studies with a total of 275 participants showed no clinically important difference between soft tissue technique and usual care. Very low quality evidence from 1 study with a total of 24 participants showed a clinically important benefit of soft tissue technique over acupuncture/dry needling at time points up to 3 months.

Sleep

Very low quality evidence from 1 study with a total of 48 participants showed a clinically important benefit of soft tissue technique over usual care at time points up to 3 months.

Discontinuation

Very low quality evidence from 1 study with a total of 52 participants showed more trial discontinuations from the soft tissue technique arm than from usual care at time points up to 3 months. Very low quality evidence from 1 study with a total of 66 participants showed no clinically important difference between soft tissue technique and usual care at time points after 3 months. Moderate quality evidence from 1 study with a total of 94 participants showed no clinically important difference between soft tissue technique and acupuncture/dry needling.

Manipulation/mobilisation versus usual care/acupuncture/dry needling

Pain reduction

Low quality evidence from 1 study with a total of 30 participants showed a clinically important benefit of manipulation/mobilisation over usual care at time points up to 3 months. Very low quality evidence from 1 study with a total of 24 participants showed no clinically important difference between manipulation/mobilisation and acupuncture/dry needling at time points up to 3 months.

Quality of life

Low quality evidence from 1 study with a total of 30 participants showed a clinically important benefit of manipulation/mobilisation over usual care at time points up to 3 months.

Physical function

Low quality evidence from 1 study with a total of 24 participants showed no clinically important difference between manipulation/mobilisation and acupuncture/dry needling at time points up to 3 months.

Psychological distress

Moderate quality evidence from 1 study with a total of 24 participants showed a clinically important benefit of manipulation/mobilisation over acupuncture/dry needling at time points up to 3 months.

Discontinuation

Very low quality evidence from 1 study with a total of 31 participants showed more trial discontinuations from the manipulation/mobilisation arm than from usual care.

Manual therapy interventions compared with each other

Pain reduction

Moderate quality evidence from 1 study with a total of 63 participants showed a clinically important benefit of mixed modality manual therapy over soft tissue technique at time points up to 3 months. Low quality evidence from 1 study with a total of 63 participants showed a clinically important benefit of mixed modality manual therapy over soft tissue technique at time points after 3 months. Low quality evidence from 1 study with a total of 30 participants showed a clinically important benefit of mixed modality manual therapy over manipulation/mobilisation at time points up to 3 months. Very low quality evidence from 3 studies with a total of 125 participants showed a clinically important benefit of manipulation/mobilisation over soft tissue technique at time points up to 3 months. Low quality evidence from 1 study with a total of 68 participants showed no clinically important difference between manipulation/mobilisation and soft tissue technique at time points after 3 months.

Quality of life

Very low quality evidence from 1 study with a total of 78 participants showed a clinically important benefit of soft tissue technique over manipulation/mobilisation for the mental component of SF12 at time points up to 3 months, but low quality evidence from the same study showed no clinically important difference between manipulation/mobilisation and soft tissue technique for the physical component.

Physical function

Very low quality evidence from 2 studies with a total of 48 participants showed a clinically important benefit of manipulation/mobilisation over soft tissue technique at time points up to 3 months. Low quality evidence from 1 study with a total of 68 participants showed no clinically important difference between manipulation/mobilisation and soft tissue technique at time points after 3 months.

Psychological distress

Low quality evidence from 1 study with a total of 24 participants showed a clinically important benefit of manipulation/mobilisation over soft tissue technique at time points up to 3 months.

Discontinuation

Very low quality evidence from 1 study with a total of 63 participants showed more discontinuations from the soft tissue technique arm than from mixed modality manual therapy. Moderate to low quality evidence from 3 studies with a total of 174 participants showed no clinically importance difference between manipulation/mobilisation and soft tissue technique.

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee considered pain reduction, health-related quality of life, physical function, psychological distress, pain interference and pain self-efficacy to be critical outcomes for decision-making. Use of healthcare services, sleep and discontinuation were also considered to be important outcomes. The critical and important outcomes agreed by the committee were adapted by consensus from relevant core outcome sets registered under the Core Outcome Measures in Effectiveness Trials (COMET) Initiative. This included the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations.

Evidence was identified for all critical outcomes, other than pain self-efficacy. Evidence for important outcomes was limited; no evidence was identified for use of healthcare services, and evidence for sleep and discontinuation was limited.

1.7.1.2 The quality of the evidence

Evidence from 15 randomised controlled trials was identified for 8 different comparisons in this review. The comparisons with the most evidence were soft tissue technique versus usual care and manipulation/mobilisation versus soft tissue technique. Only a small amount of evidence was found for the other comparisons identified. No evidence was identified for traction against any comparator, or for manipulation/mobilisation compared with usual care.

The majority of the evidence in this review was of low to very low quality, with only 3 outcomes supported by evidence of moderate quality. Evidence was mostly downgraded due to risk of bias and imprecision. Risk of bias was most commonly due to selection and blinding bias. As comparator groups received either a different intervention or usual care, there was often no participant or investigator blinding in studies. Combined with the subjective nature of

the outcomes, this was deemed to create a high risk of bias. Due to the nature of the manual therapy interventions and difficulty of delivering a feasible placebo, sham intervention comparators were excluded. The low quality of evidence was taken into consideration by the committee when assessing the small evidence base in this review.

The manual therapy interventions included in this review varied in their type and intensity. The committee noted that there was potential for crossover between soft tissue techniques and manipulation/mobilisation; for example, vigorous or forceful massage might be very close in practice to other manual therapy techniques that are here classified as manipulation. It was also observed that there was significant variation between mixed manual therapy interventions. It was therefore suggested that this could be a further limitation of the evidence base presented for comparisons in this review.

1.7.1.3 Benefits and harms

Mixed modality manual therapy versus usual care

There was evidence for 3 outcomes under this comparison, taken from two studies (n=70). The quality of evidence for this comparison ranged from low to very low, primarily due to risk of bias and imprecision. All 3 of these outcomes were reported at less than 3 months: pain reduction, physical function and discontinuation. Mixed modality manual therapy showed a clinically important benefit over usual care for pain reduction measured on a visual analogue scale, although there was uncertainty around the evidence. No clinically important difference was observed for pain reduction on the Brief Pain Inventory. There was a benefit of mixed modality manual therapy for physical function. Trial discontinuation was more likely to occur in usual care than mixed modality manual therapy. Outcomes also reported at time points over 3 months were pain reduction on the Brief Pain Inventory and physical function, which both showed a benefit of mixed modality manual therapy, although there was some uncertainty around the effect estimate for pain reduction.

Soft tissue technique versus usual care

In this comparison there was evidence for 6 outcomes at less than 3 months: pain reduction, health-related quality of life, physical function, psychological distress, sleep and discontinuation. All evidence was either of low or very low quality, mainly due to risk of bias and imprecision. Some outcomes were downgraded for indirectness of the comparator, as half of the usual care group also took part in group discussions. Soft tissue technique showed benefit over usual care for pain reduction, health-related quality of life (Fibromyalgia Impact Questionnaire), physical function (Neck Disability Index), psychological distress (depression), and sleep disturbance, with some uncertainty. No clinically important difference was seen for health-related quality of life (SF-12 mental health component), physical function (Disability Rating Index), psychological distress (anxiety) or psychological distress (Perceived Stress Scale) at this time point. There were more discontinuations in the group receiving soft tissue technique than usual care at less than 3 months. Over 3 months there was benefit observed in the soft tissue technique group for health-related quality of life and discontinuation, but there was uncertainty around the effect estimates and no evidence for any other outcomes at this time point.

Manipulation/mobilisation versus usual care

Evidence from 1 study showed a benefit of manipulation/mobilisation for pain reduction and quality of life at 3 months. The evidence was of low quality due to risk of bias and imprecision. There were more study discontinuations in the manipulation/mobilisation group.

Mixed modality manual therapy versus soft tissue technique

There was only evidence for pain reduction (at both short and longer term follow up) and discontinuation at less than 3 months. The evidence for pain reduction at less than 3 months

was moderate quality (the highest quality of evidence in this review) which was only downgraded for risk of bias, while the other outcomes were low and very low quality, respectively, due to risk of bias and imprecision. All 3 outcomes showed benefit of mixed modality manual therapy over soft tissue technique. These outcomes were taken from 1 study (63 participants).

Mixed modality manual therapy versus manipulation/mobilisation

In this comparison there was only evidence for 1 outcome; pain reduction at less than 3 months. This evidence was from 1 small study and was rated as low quality due to risk of bias and imprecision. For this single post-treatment (3 weeks) outcome, the limited evidence showed a benefit of mixed manual therapy over manipulation/mobilisation.

Manipulation/mobilisation versus soft tissue technique

There was evidence for 5 outcomes in this comparison, from 4 studies. The quality of evidence was low to very low, due to risk of bias, imprecision and inconsistency. For pain reduction and physical function, there was a benefit of manipulation/mobilisation at time points up to 3 months, but there was some uncertainty around the effect estimates and there was no clinically important difference at longer than 3 months. Evidence for quality of life at up to 3 months showed no difference in the physical component, but a benefit of soft tissue technique in the mental component with some uncertainty. Evidence showed a benefit of manipulation/mobilisation for psychological distress at less than 3 months. Discontinuation showed no clinically important difference at less than 3 months, but there were fewer discontinuations in people receiving manipulation/mobilisation than soft tissue technique beyond 3 months.

Mixed modality manual therapy versus dry needling/acupuncture

There were 3 outcomes for this comparison, all taken from 1 small study and all at less than 3 months: pain reduction, physical function and psychological distress. The quality of this evidence was low or very low, due to risk of bias and imprecision. There was a benefit of acupuncture/dry needling for physical function, but no clinically important difference for the other 2 outcomes.

Soft tissue technique versus dry needling/acupuncture

There were 4 outcomes for this comparison, all reported at less than 3 months: pain reduction, physical function, psychological distress and discontinuation. The quality of evidence for these outcomes ranged from low to very low due to risk of bias and imprecision, with moderate quality evidence for discontinuation. There was a benefit of acupuncture/dry needling for pain reduction and physical function, but a benefit of soft tissue technique for psychological distress. There was no clinically important difference for discontinuation.

Manipulation/mobilisation versus dry needling/acupuncture

In this comparison there were 3 outcomes, all reported at less than 3 months: pain reduction, physical function and psychological distress. The quality of evidence for psychological distress was moderate, while physical function had low quality evidence and pain reduction had very low quality evidence (both downgraded for risk of bias and imprecision). Pain reduction and physical function showed no clinically important difference, but there was a benefit of manipulation/mobilisation over acupuncture/dry needling for psychological distress.

Overall

The committee acknowledged that the evidence base for each comparison was limited and insufficient to justify a recommendation for any specific type of manual therapy. However, considering the evidence comparing manual therapies with usual care overall, the committee agreed that the benefits to critical outcomes were promising. In additional, there was no

evidence of harm, although the committee noted that harms and reasons for discontinuation are often poorly reported by the trials. While the committee were unable to draw conclusions about the optimal type of manual therapy from the evidence, the committee did decide to recommend further research to answer this question.

1.7.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

The costs of physiotherapy staff were presented to the committee, as these are the staff that might provide manual therapy.

Manual therapy is not commonly used in the NHS for the management of chronic primary pain. The overall amount of evidence identified for this review was small, and the committee agreed there was not enough evidence of benefit to warrant a positive recommendation. However, there was also no evidence of harm to recommend against using manual therapies. Therefore a research recommendation has been made rather than a practice recommendation as the evidence base included for this question was not considered sufficient to warrant NHS resources being diverted from other areas to manual therapy.

1.7.3 Other factors the committee took into account

The committee discussed the overlap of different categories of manual therapy included in the review, for example massage is a type of soft tissue technique but could be classed as manipulation if it is deep enough. This also contributed to the difficulty in determining the optimal type of manual therapy.

Clinically, within manual therapies, there would be different considerations for different types of pain for example people with fibromyalgia may not like to be touched, neck massage may be more effective for those with neck pain than orofacial pain. This might not be reflected in the evidence presented in this review as in many cases there was only a single study available for a comparison and so it cannot be determined whether there would have been heterogeneity. In the few cases where evidence could be meta-analysed in this review, heterogeneity (where present) was not explained with subgroup analysis by type of chronic pain. However the committee agreed there was insufficient evidence to identify whether there was variation in the effect by type of chronic primary pain. This is recognised as an area to consider in the research recommendation.

The committee considered that manual therapies are not commonly used for chronic primary pain in NHS settings and noted that chronic primary pain sufferers have often sought manual therapy privately for personal pain management.

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Appendices

Appendix A: Review protocols

Review protocol for manual therapies

ID	Field	Content
0.	PROSPERO registration number	Not registered.
1.	Review title	What is the clinical and cost effectiveness of manual therapy for the management of chronic primary pain?
2.	Review question	What is the clinical and cost effectiveness of manual therapy for the management of chronic primary pain?
3.	Objective	To determine the clinical and cost effectiveness of manual therapy for the management of chronic primary pain.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • CINAHL, Current Nursing and Allied Health Literature. 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 committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) and functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms.
6.	Population	Inclusion: People, aged 16 years and over, with chronic primary pain (whose pain management is not addressed by existing NICE guidance) (chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain , chronic primary musculoskeletal pain other than orofacial) Exclusion: Those whose pain management is addressed by existing NICE guidance.
7.	Intervention/Exposure/Test	Interventions: • soft tissue technique (e.g. massage, muscle energy technique, myofascial/trigger point release) • traction • manipulation/mobilisation (including spinal manipulation therapy [SMT] and Maitland technique) • mixed modality manual therapy (soft tissue technique +/- traction +/- manipulation/mobilisation).
8.	Comparator/Reference standard/Confounding factors	Comparators: • each other • usual care • acupuncture/dry needling.

9.	Types of study to be included	Randomised controlled trials (RCTs) and systematic reviews of RCTs Cross-over RCTs will be considered if no non-cross-over RCT evidence is identified.
10.	Other exclusion criteria	Non-English language studies. Studies comparing combinations of interventions.
11.	Context	A clear understanding of the evidence for the effectiveness of chronic primary pain treatments: • improves the confidence of healthcare professionals in their conversations about pain, and • helps healthcare professionals and patients to have realistic expectations about outcomes of treatment.
12.	Primary outcomes (critical outcomes)	• Pain reduction (any validated scale) • health related quality of life (including meaningful activity) • physical function (5 minute walk, sit to stand, Roland Morris Disability Questionnaire, Oswestry Disability Index, Canadian Occupational Performance Measure) • psychological distress (depression/anxiety) (preferably Hospital Anxiety and Depression Scale) • pain interference (brief pain inventory interference subscale) • pain self-efficacy (pain self-efficacy questionnaire). Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months.
13.	Secondary outcomes (important outcomes)	• Use of healthcare services • sleep • discontinuation. Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months.
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 Cochrane Risk of Bias (2.0) tool. 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.	
17.	Analysis of sub-groups	Proposed sensitivity / subgroup analysis to be explored where there is heterogeneity: • chronic widespread pain • complex regional pain syndrome • chronic visceral pain • chronic orofacial pain • chronic primary musculoskeletal pain • cognitive impairment • learning difficulties • first language not English • sensory impairment • homelessness.	
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	NA – not registered on PROSPERO	
22.	Anticipated completion date	19/08/2020	
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Chronicpain@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	
24.	Review team members	From the National Guideline Centre: Serena Carville, Guideline Lead Maria Smyth, Senior Systematic Reviewer Rebecca Boffa, Senior Systematic Reviewer	

		Margaret Constanti, Senior Health Economist Joseph Runicles, Information Specialist Katie Broomfield, Project Manager
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	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.
27.	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-ng10069
28.	Other registration details	NA
29.	Reference/URL for published protocol	NA
30.	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.

31.	Keywords	-
32.	Details of existing review of same topic by same authors	NA
33.	Additional information	-
34.	Details of final publication	www.nice.org.uk

Table 13: 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 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 2002. Abstract-only studies and studies from non-OECD countries or the USA will also be excluded. 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).[194] **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 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 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.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[194]

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

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 May 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 20 May 2020	Exclusions Randomised controlled trials Systematic review studies

Database	Dates searched	Search filter used
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 5 of 12 CENTRAL to 2020 Issue 5 of 12	None
AMED (Allied and Complementary Medicine)	1985 – 20 May 2020	Exclusions Randomised controlled trials Systematic review studies

Medline (Ovid) search terms

1.	Chronic pain/
2.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
3.	exp Complex Regional Pain Syndromes/
4.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
5.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
6.	fibromyalgia/
7.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	exp myofascial pain syndromes/
15.	cystitis, interstitial/
16.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
17.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
18.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
19.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
20.	(temporomandibular adj3 joint adj3 pain).ti,ab.
21.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
22.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
23.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
24.	or/1-23
25.	letter/
26.	editorial/
27.	news/
28.	exp historical article/
29.	Anecdotes as Topic/
30.	comment/
31.	case report/
32.	(letter or comment*).ti.
33.	or/25-32
34.	randomized controlled trial/ or random*.ti,ab.
35.	33 not 34
36.	animals/ not humans/

37.	exp Animals, Laboratory/
38.	exp Animal Experimentation/
39.	exp Models, Animal/
40.	exp Rodentia/
41.	(rat or rats or mouse or mice).ti.
42.	or/35-41
43.	24 not 42
44.	limit 43 to English language
45.	exp Musculoskeletal Manipulations/
46.	((musculoskeletal or musculo skeletal or physical) adj (manipulat* or therap* or treat)).ti,ab.
47.	(muscle* energy adj (technique* or therap*)).ti,ab.
48.	((autogenic or reciprocal) adj inhibition).ti,ab.
49.	(isometric relax* or facilitat* stretch*).ti,ab.
50.	(massag* or rolfing or structural integration or myotherapy).ti,ab.
51.	((myofascial or trigger or soft tissue) adj3 (therap* or release)).ti,ab.
52.	(acupressure or shiat#u or chih ya or zhi ya or kinesiology or chiropract* or bodywork or body work or reflexolog*).ti,ab.
53.	((manual or mobili* or zone or manipulat*) adj3 (therap* or treat* or technique*)).ti,ab.
54.	((osteopath* or chiropract* or manual* or ortho*) adj3 (manipulat* or mobili* or adjust*)).ti,ab.
55.	((spine or spinal or lumbosacral or lumbo-sacral or lumbar) adj3 (manipulat* or mobili* or adjust*)).ti,ab.
56.	(maitland adj (concept or technique)).ti,ab.
57.	Traction/
58.	traction*.ti,ab.
59.	or/45-58
60.	randomized controlled trial.pt.
61.	controlled clinical trial.pt.
62.	randomi#ed.ti,ab.
63.	placebo.ab.
64.	randomly.ti,ab.
65.	Clinical Trials as topic.sh.
66.	trial.ti.
67.	or/60-66
68.	Meta-Analysis/
69.	exp Meta-Analysis as Topic/
70.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
71.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
72.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
73.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
74.	(search* adj4 literature).ab.
75.	(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.
76.	cochrane.jw.
77.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
78.	or/68-77

79.	44 and 59
80.	79 and (67 or 78)

Embase (Ovid) search terms

1.	Chronic pain/
2.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
3.	exp Complex regional pain syndrome/
4.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
5.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
6.	fibromyalgia/
7.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	myofascial pain/
15.	noncardiac chest pain/
16.	cystalgia/
17.	Pelvis pain syndrome/
18.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
19.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
20.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
21.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
22.	(temporomandibular adj3 joint adj3 pain).ti,ab.
23.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
24.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
25.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
26.	or/1-25
27.	letter.pt. or letter/
28.	note.pt.
29.	editorial.pt.
30.	case report/ or case study/
31.	(letter or comment*).ti.
32.	or/27-31
33.	randomized controlled trial/ or random*.ti,ab.
34.	32 not 33
35.	animal/ not human/
36.	nonhuman/
37.	exp Animal Experiment/
38.	exp Experimental Animal/
39.	animal model/
40.	exp Rodent/
41.	(rat or rats or mouse or mice).ti.

42.	or/34-41
43.	26 not 42
44.	limit 43 to English language
45.	exp manipulative medicine/
46.	exp *soft tissue/
47.	exp *physiotherapy/
48.	((musculoskeletal or musculo skeletal or physical) adj (manipulat* or therap* or treat)).ti,ab.
49.	(muscle* energy adj (technique* or therap*)).ti,ab.
50.	((autogenic or reciprocal) adj inhibition).ti,ab.
51.	(isometric relax* or facilitat* stretch*).ti,ab.
52.	(massag* or rolfing or structural integration or myotherapy).ti,ab.
53.	((myofascial or trigger or soft tissue) adj3 (therap* or release)).ti,ab.
54.	(acupressure or shiat#u or chih ya or zhi ya or kinesiology or chiropract* or bodywork or body work or reflexolog*).ti,ab.
55.	((manual or mobili* or zone or manipulat*) adj3 (therap* or treat* or technique*)).ti,ab.
56.	((osteopath* or chiropract* or manual* or ortho*) adj3 (manipulat* or mobili* or adjust*)).ti,ab.
57.	((spine or spinal or lumbosacral or lumbo-sacral or lumbar) adj3 (manipulat* or mobili* or adjust*)).ti,ab.
58.	(maitland adj (concept or technique)).ti,ab.
59.	Traction/
60.	traction*.ti,ab.
61.	or/48-60
62.	random*.ti,ab.
63.	factorial*.ti,ab.
64.	(crossover* or cross over*).ti,ab.
65.	((doubl* or singl*) adj blind*).ti,ab.
66.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
67.	crossover procedure/
68.	single blind procedure/
69.	randomized controlled trial/
70.	double blind procedure/
71.	or/62-70
72.	systematic review/
73.	meta-analysis/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(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.
80.	cochrane.jw.
81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	44 and 61 and (71 or 82)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Chronic Pain] explode all trees
#2.	((chronic or persist* or idiopathic or atypical or a-typical) near/4 pain):ti,ab
#3.	MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees
#4.	(complex regional pain syndrome* or CRPS or causalgia):ti,ab
#5.	((reflex or sympathetic) near/2 dystroph*):ti,ab
#6.	MeSH descriptor: [Fibromyalgia] explode all trees
#7.	(fibromyalgia* or fibrositis or myofascial pain syndrome):ti,ab
#8.	MeSH descriptor: [Vulvodynia] explode all trees
#9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis):ti,ab
#10.	MeSH descriptor: [Cystitis, Interstitial] explode all trees
#11.	(interstitial near/2 cystitis):ti,ab
#12.	MeSH descriptor: [Reflex Sympathetic Dystrophy] explode all trees
#13.	(algodystroph* or sudek or sudeck*):ti,ab
#14.	MeSH descriptor: [Myofascial Pain Syndromes] explode all trees
#15.	(loinpain near (haematuria or hematuria) near syndrome*):ti,ab
#16.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS):ti,ab
#17.	((pelvic or pelvis) near pain syndrome*):ti,ab
#18.	((non-cardiac or noncardiac) near/3 chest near/3 pain):ti,ab
#19.	(temporomandibular near/3 joint near/3 pain):ti,ab
#20.	((prostate or vulv* or bladder or perineal) near/3 pain):ti,ab
#21.	(functional pain syndrome* or non-cancer pain or noncancer pain):ti,ab
#22.	((pelvic or pelvis or abdominal) near/3 pain near/3 (unknown or un-known or idiopathic or atypic* or a-typic*)):ti,ab
#23.	(or #1-#22)
#24.	MeSH descriptor: [Musculoskeletal Manipulations] explode all trees
#25.	((musculoskeletal or musculo skeletal or physical) near (manipulat* or therap* or treat)):ti,ab
#26.	(muscle*energy near (technique* or therap*)):ti,ab
#27.	((autogenic or reciprocal) near inhibition):ti,ab
#28.	(isometric relax* or facilitat* stretch*):ti,ab
#29.	(massag* or rolfing or structural integration or myotherapy):ti,ab
#30.	((myofascial or trigger or soft tissue) near/3 (therap* or release)) ti,ab
#31.	(acupressure or shiat?u or chih ya or zhi ya or kinesiology or chiropract* or bodywork or body work or reflexolog*):ti,ab
#32.	((manual or mobili* or zone or manipulat*) near/3 (therap* or treat* or technique*)):ti,ab
#33.	((osteopath* or chiropract* or manual* or ortho*) near/3 (manipulat* or mobili* or adjust*)):ti,ab
#34.	((spine or spinal or lumbosacral or lumbo-sacral or lumbar) near/3 (manipulat* or mobili* or adjust*)):ti,ab
#35.	(maitland near (concept or technique)):ti,ab
#36.	MeSH descriptor: [Traction] explode all trees
#37.	traction*:ti,ab
#38.	(or #24-#37)
#39.	#23 and #38

AMED (Ovid) search terms

1.	pain intractable/
2.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
3.	exp complex regional pain syndromes/
4.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
5.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
6.	fibromyalgia/
7.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
8.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
9.	cystitis/
10.	(interstitial adj2 cystitis).ti,ab.
11.	(algodystroph* or sudek or sudeck*).ti,ab.
12.	exp myofascial pain syndromes/
13.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
14.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
15.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
16.	(temporomandibular adj3 joint adj3 pain).ti,ab.
17.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
18.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
19.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
20.	or/1-19
21.	case report/
22.	(letter or comment*).ti.
23.	or/21-22
24.	randomized controlled trials/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	(rat or rats or mouse or mice).ti.
28.	or/25-27
29.	20 not 28
30.	randomized controlled trials/
31.	randomized controlled trial.pt.
32.	controlled clinical trial.pt.
33.	placebo.ab.
34.	random*.ti,ab.
35.	trial.ti,ab.
36.	groups.ab.
37.	or/30-36
38.	Meta-Analysis/
39.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
40.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
41.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
42.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
43.	(search* adj4 literature).ab.

44.	(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.
45.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
46.	or/38-45
47.	29 and (37 or 46)
48.	exp Musculoskeletal manipulations/
49.	Traction/
50.	massage/ or exp mobilisation/
51.	soft tissue/
52.	exp physical therapy modalities/
53.	((musculoskeletal or musculo skeletal or physical) adj (manipulat* or therap* or treat)).ti,ab.
54.	(muscle* energy adj (technique* or therap*)).ti,ab.
55.	((autogenic or reciprocal) adj inhibition).ti,ab.
56.	(isometric relax* or facilitat* stretch*).ti,ab.
57.	(massag* or rolfing or structural integration or myotherapy).ti,ab.
58.	((myofascial or trigger or soft tissue) adj3 (therap* or release)).ti,ab.
59.	(acupressure or shiat#u or chih ya or zhi ya or kinesiology or chiropract* or bodywork or body work or reflexolog*).ti,ab.
60.	((manual or mobili* or zone or manipulat*) adj3 (therap* or treat* or technique*)).ti,ab.
61.	((osteopath* or chiropract* or manual* or ortho*) adj3 (manipulat* or mobili* or adjust*)).ti,ab.
62.	((spine or spinal or lumbosacral or lumbo-sacral or lumbar) adj3 (manipulat* or mobili* or adjust*)).ti,ab.
63.	(maitland adj (concept or technique)).ti,ab.
64.	traction*.ti,ab.
65.	or/48-64
66.	47 and 65

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Chronic Pain population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. 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 and economic modelling.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 20 May 2020	Exclusions Health economics studies Health economics modelling studies
Embase	2014 – 20 May 2020	Exclusions Health economics studies Health economics modelling studies

Database	Dates searched	Search filter used
Centre for Research and Dissemination (CRD)	HTA - Inception – 30 September 2019 NHSEED - Inception to March 2015	None

Medline search terms

1.	chronic pain/ or pain, intractable/
2.	((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab.
3.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
4.	exp Complex Regional Pain Syndromes/
5.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
6.	fibromyalgia/
7.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	exp myofascial pain syndromes/
15.	cystitis, interstitial/
16.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
17.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
18.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
19.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
20.	(temporomandibular adj3 joint adj3 pain).ti,ab.
21.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
22.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
23.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
24.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
25.	or/1-24
26.	letter/
27.	editorial/
28.	news/
29.	exp historical article/
30.	Anecdotes as Topic/
31.	comment/
32.	case report/
33.	(letter or comment*).ti.
34.	or/26-33
35.	randomized controlled trial/ or random*.ti,ab.

36.	34 not 35
37.	animals/ not humans/
38.	exp Animals, Laboratory/
39.	exp Animal Experimentation/
40.	exp Models, Animal/
41.	exp Rodentia/
42.	(rat or rats or mouse or mice).ti.
43.	or/36-42
44.	25 not 43
45.	Economics/
46.	Value of life/
47.	exp "Costs and Cost Analysis"/
48.	exp Economics, Hospital/
49.	exp Economics, Medical/
50.	Economics, Nursing/
51.	Economics, Pharmaceutical/
52.	exp "Fees and Charges"/
53.	exp Budgets/
54.	budget*.ti,ab.
55.	cost*.ti.
56.	(economic* or pharmaco?economic*).ti.
57.	(price* or pricing*).ti,ab.
58.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
59.	(financ* or fee or fees).ti,ab.
60.	(value adj2 (money or monetary)).ti,ab.
61.	or/45-60
62.	exp models, economic/
63.	*Models, Theoretical/
64.	*Models, Organizational/
65.	markov chains/
66.	monte carlo method/
67.	exp Decision Theory/
68.	(markov* or monte carlo).ti,ab.
69.	econom* model*.ti,ab.
70.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
71.	or/62-70
72.	44 and (61 or 71)

Embase (Ovid) search terms

1.	chronic pain/ or pain, intractable/
2.	((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab.
3.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
4.	exp Complex regional pain syndrome/
5.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
6.	((reflex or sympathetic) adj2 dystroph*).ti,ab.

7.	fibromyalgia/
8.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
9.	vulvodynia/
10.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
11.	interstitial cystitis/
12.	(interstitial adj2 cystitis).ti,ab.
13.	algodystrophy/
14.	(algodystroph* or sudek or sudeck*).ti,ab.
15.	myofascial pain/
16.	noncardiac chest pain/
17.	cystalgia/
18.	Pelvis pain syndrome/
19.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
20.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
21.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
22.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
23.	(temporomandibular adj3 joint adj3 pain).ti,ab.
24.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
25.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
26.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
27.	or/1-26
28.	letter.pt. or letter/
29.	note.pt.
30.	editorial.pt.
31.	case report/ or case study/
32.	(letter or comment*).ti.
33.	or/28-32
34.	randomized controlled trial/ or random*.ti,ab.
35.	33 not 34
36.	animal/ not human/
37.	nonhuman/
38.	exp Animal Experiment/
39.	exp Experimental Animal/
40.	animal model/
41.	exp Rodent/
42.	(rat or rats or mouse or mice).ti.
43.	or/35-42
44.	27 not 43
45.	health economics/
46.	exp economic evaluation/
47.	exp health care cost/
48.	exp fee/
49.	budget/
50.	funding/
51.	budget*.ti,ab.

52.	cost*.ti.
53.	(economic* or pharmaco?economic*).ti.
54.	(price* or pricing*).ti,ab.
55.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
56.	(financ* or fee or fees).ti,ab.
57.	(value adj2 (money or monetary)).ti,ab.
58.	or/45-57
59.	statistical model/
60.	exp economic aspect/
61.	59 and 60
62.	*theoretical model/
63.	*nonbiological model/
64.	stochastic model/
65.	decision theory/
66.	decision tree/
67.	monte carlo method/
68.	(markov* or monte carlo).ti,ab.
69.	econom* model*.ti,ab.
70.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
71.	or/61-70
72.	44 and (58 or 71)

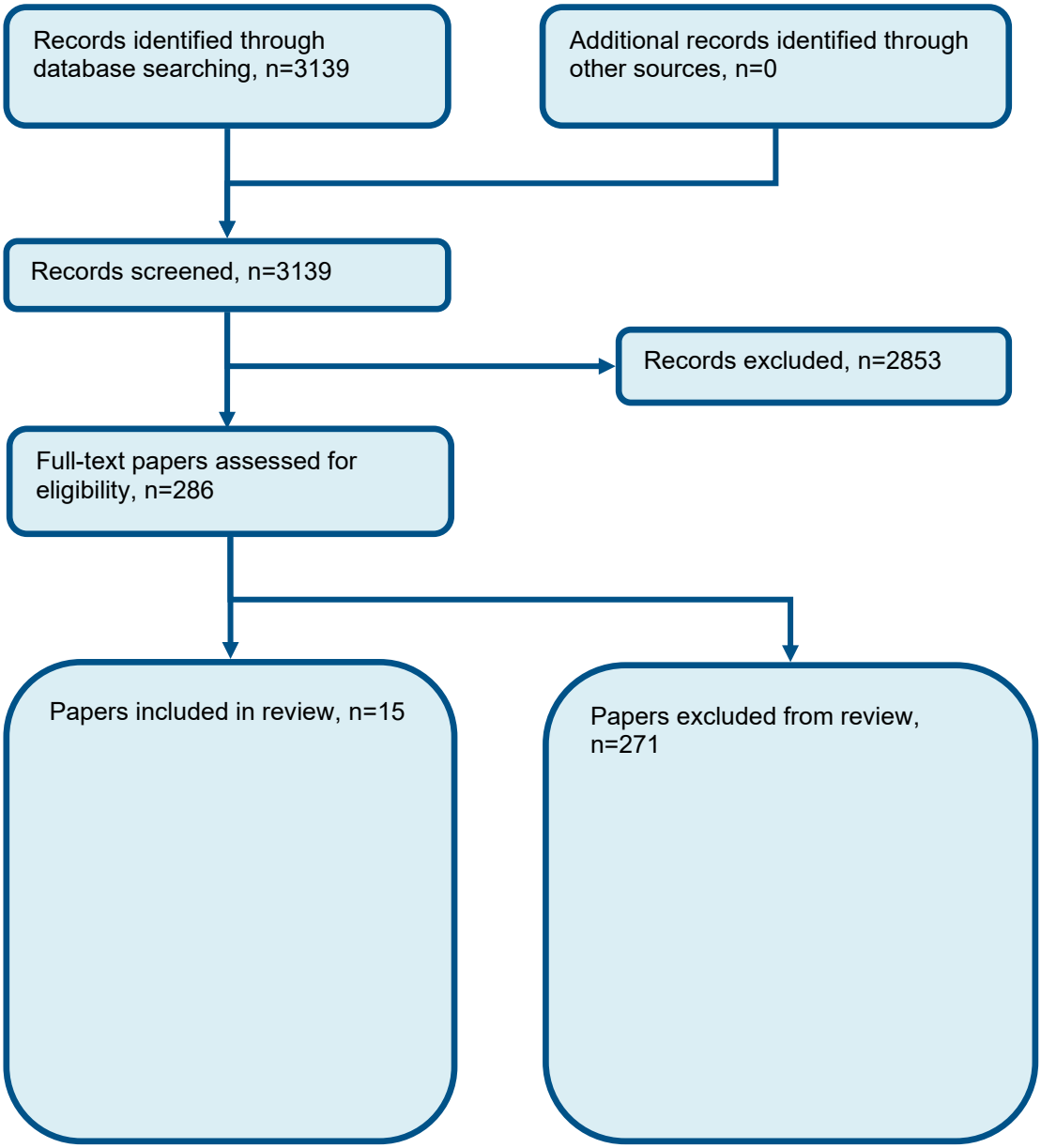
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Chronic Pain EXPLODE ALL TREES
#2.	(((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*))
#3.	(((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain))
#4.	MeSH DESCRIPTOR Complex Regional Pain Syndromes EXPLODE ALL TREES
#5.	((complex regional pain syndrome* or CRPS or causalgia))
#6.	MeSH DESCRIPTOR Fibromyalgia EXPLODE ALL TREES
#7.	(((reflex or sympathetic) adj2 dystroph*))
#8.	MeSH DESCRIPTOR Vulvodynia EXPLODE ALL TREES
#9.	((vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis))
#10.	MeSH DESCRIPTOR Cystitis, Interstitial EXPLODE ALL TREES
#11.	((interstitial adj2 cystitis))
#12.	MeSH DESCRIPTOR Reflex Sympathetic Dystrophy EXPLODE ALL TREES
#13.	((algodystroph* or sudek or sudeck*))
#14.	MeSH DESCRIPTOR Myofascial Pain Syndromes EXPLODE ALL TREES
#15.	((loin pain adj (haematuria or hematuria) adj syndrome*))
#16.	((LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS))
#17.	(((pelvic or pelvis) adj pain syndrome*))
#18.	(((non-cardiac or noncardiac) adj3 chest adj3 pain))
#19.	((temporomandibular adj3 joint adj3 pain))
#20.	(((prostate or vulv* or bladder or perineal) adj3 pain))
#21.	((functional pain syndrome* or non-cancer pain or noncancer pain))

#22.	(((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)))
#23.	((fibromyalgia* or fibrositis or myofascial pain syndrome))
#24.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of manual therapy for chronic primary pain



Appendix D: Clinical evidence tables

Study	Albers 2018[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Germany; Setting: single centre, no further details
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR diagnostic criteria for fibromyalgia
Stratum	Overall: NA
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	>18 years of age; medically diagnosed with fibromyalgia by their GP by fulfilling the ACR criteria; average pain intensity >4 on VAS within the last 3 months
Exclusion criteria	manual therapy or alternative treatment during the study; systemic conditions such as cancer, severe OA, RA or systemic lupus erythematosus; viral infections; hypothyroidism, chronic fatigue syndrome, myositis and myoneuropathies
Recruitment/selection of patients	word of mouth, flyers, advertisements in rehabilitation, pain medicine and rheumatology practices, posters in doctors' offices, pharmacies and sports clubs
Age, gender and ethnicity	Age - Mean (SD): osteopathic treatment 55.4 (11.9), control 53.8 (16.3) years. Gender (M:F): 0/31. Ethnicity: not reported
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: No 3. Chronic visceral pain: No 4. Chronic widespread pain: Yes 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=17) Intervention 1: Manual therapy - Manipulation/mobilisation. General osteopathic treatment - 10 x 45 minute weekly sessions. Large but gentle movements performed continuously and rhythmically, mobilizing dysfunctional areas of the body in a well-defined order. Slow mobilisation of the soft tissues and articular techniques are incorporated, adapted to the needs of the patient. Duration 12 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA

Study	Albers 2018[5]
	(n=14) Intervention 2: Usual care. Control - remained untreated during the study period. Duration 12 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANIPULATION/MOBILISATION versus USUAL CARE Protocol outcome 1: Pain reduction - Actual outcome: Pain visual analogue scale at 12 weeks ; Group 1: mean 4.3 (SD 2.3); n=16, Group 2: mean 6.6 (SD 1.9); n=14; VAS 0-10 Top=High is poor outcome; Comments: Baseline values: osteopathic treatment 6.3 (1.2), control 6.2 (1.6) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: discontinued ; Group 2 Number missing: 0, Reason: NA Protocol outcome 2: Health related quality of life - Actual outcome: Fibromyalgia Impact Questionnaire at 12 weeks ; Group 1: mean 40.1 (SD 21.2); n=16, Group 2: mean 51.8 (SD 16.3); n=14; Fibromyalgia Impact Questionnaire 0-100 Top=High is poor outcome; Comments: Baseline values: osteopathic treatment 55.6 (15.9), control 54.3 (18.8) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: discontinued ; Group 2 Number missing: 0, Reason: NA Protocol outcome 3: Discontinuation - Actual outcome: Discontinuation at 12 weeks ; Group 1: 1/17, Group 2: 0/14; Comments: not able to cope with the study demands Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA	
Protocol outcomes not reported by the study	Physical function; Psychological distress; Pain interference; Pain self-efficacy; Use of healthcare services; Sleep

Study	Ariza-Mateos 2019[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=49)
Countries and setting	Conducted in Spain; Setting:
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 weeks + 3 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Patients diagnosed with chronic pelvic pain (CPP)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria were female sex, age between 18 and 65 years, diagnosis of chronic pelvic pain (CPP) with at least 6 months of evolution and the presence of fear of movement evaluated with the Tampa Scale for Kinesiophobia (score >33).
Exclusion criteria	The exclusion criteria were: other syndromes and/or diseases involving chronic pain, active urogenital infection, pregnancy, prior urogenital malignancy, cancer, surgical intervention involving lumbo-pelvic region over the past year, vaginal prolapsed exceeding second degree, chronic fatigue syndrome, fibromyalgia, psychiatric disorders, dementia, and substance abuse interfering with treatment.
Recruitment/selection of patients	Participants were recruited from the Gynaecology Service of a University Hospital in Granada (Spain) from September 2017 to January 2018.
Age, gender and ethnicity	Age - Mean (SD): MT group 40.67 (11.7); Control group 42.40 (6.15). Gender (M:F): All women. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: No 3. Chronic visceral pain: Yes 4. Chronic widespread pain: No 5. Cognitive impairment: No 6. Complex regional pain syndrome: No 7. First language not English: No 8. Homeless: No 9. Learning difficulties: No 10. Sensory impairment: No
Extra comments	There were three experimental arms: Graded exposure therapy (GET) + manual therapy (MT) (n=16) Manual therapy (MT) alone (n=16) Control group (waiting list) (n=17) Mean years duration of pain (SD): manual therapy group 9.58 (5.38), control group 7.27 (5.35)
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Manual therapy - Mixed modality manual therapy. All the women included in the manual therapy (MT) group received an intervention of 45 minutes, twice per week, consisting of manual

Study	Ariza-Mateos 2019[20]
	techniques to increase flexibility, decrease trigger point-related pain, reduce tension, and increase balance and stability. Each session included soft tissue mobilisations and myofascial release (20min) to improve circulation, restore tissue integrity, decrease ischemia, and decrease adverse neural tension. This was combined with deep-pressure massage (15min) to reduce trigger point-related pain and tension. In addition, muscle energy techniques (10min) were used to strengthen weak muscles and to stretch tight muscles, and to promote joint muscle balance and stability. The duration of each technique was adapted to the patient's tissue response. Duration Twice weekly for 6 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=17) Intervention 2: Usual care. Waiting list control. The women included in the control group received a booklet with chronic pelvic pain information to minimize potential dropout. Duration 6 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MODALITY MANUAL THERAPY versus USUAL CARE

Protocol outcome 1: Pain reduction
- Actual outcome: Pain severity on the Brief Pain Inventory (BPI) at Post-treatment (6 weeks); Group 1: mean 4.5 (SD 1.78); n=16, Group 2: mean 4.63 (SD 2.75); n=17; Brief Pain Inventory 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): MT group 5.83 (2.02) Control group 5.14 (1.66)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in baseline for Brief Pain Inventory pain interference score and daily activity minutes.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain severity on the Brief Pain Inventory (BPI) at 3 months after treatment (18 weeks); Group 1: mean 4.08 (SD 1.16); n=16, Group 2: mean 6 (SD 1.89); n=17; Brief Pain Inventory 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): MT group 5.83 (2.02) Control group 5.14 (1.66)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in baseline for Brief Pain Inventory pain interference score and daily activity minutes.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Physical function
- Actual outcome: Oswestry Disability Index at Post-treatment (6 weeks); Group 1: mean 21.82 (SD 12.02); n=16, Group 2: mean 33.33 (SD 14.02); n=17; Oswestry Disability Index 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): MT group 31.4 (8.17) Control group 30.5 (17.66)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in baseline for Brief Pain Inventory pain interference score and daily activity minutes.; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Ariza-Mateos 2019[20]
- Actual outcome: Oswestry Disability Index at 3 months after treatment (18 weeks); Group 1: mean 11.92 (SD 6.71); n=16, Group 2: mean 28.7 (SD 11.88); n=17; Oswestry Disability Index 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): MT group 31.4 (8.17) Control group 30.5 (17.66) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in baseline for Brief Pain Inventory pain interference score and daily activity minutes.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Pain interference -Actual outcome: Brief pain inventory (pain interference) at Post-treatment (6 weeks); Group 1: mean 5.06 (SD 1.53); n=16, Group 2 mean 4.72 (SD 3.03); n=17; Brief pain inventory interference 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): MT group 6.48 (1.49) Control group 4.76 (2.36) Risk of bias: All domain – Very high, Selection – High, Blinding – High, Incomplete outcome data – Low, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: No indirectness; Baseline details: Difference in baseline for Brief Pain Inventory pain interference score and daily activity minutes.; Group 1 Number missing: 0; Group 2 Number missing: 0 -Actual outcome: Brief pain inventory (pain interference) at 3 months after treatment (18 weeks); Group 1: mean 5.73 (SD 0.65); n=16, Group 2 mean 45.09 (SD 1.51); n=17; Brief pain inventory interference 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): MT group 6.48 (1.49) Control group 4.76 (2.36) Risk of bias: All domain – Very high, Selection – High, Blinding – High, Incomplete outcome data – Low, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: No indirectness; Baseline details: Difference in baseline for Brief Pain Inventory pain interference score and daily activity minutes.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health related quality of life ; Psychological distress ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Blunt 1997[34]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=21)
Countries and setting	Conducted in Canada; Setting: The chiropractic program took place at a chiropractic and rehabilitation center.
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients fulfilled the American College of Rheumatology's 1990 criteria for the classification of fibromyalgia, as assessed by the referring physician.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were included if they were between the ages of 18 and 70 and fulfilled the American College of Rheumatology's 1990 criteria for the classification of fibromyalgia, as assessed by the referring physician.
Exclusion criteria	Patients were excluded from participating in the study for any of the following reasons: 1) comorbidity, such as neurological, traumatic, muscular, infectious, osseous or endocrinological condition, that may prevent attendance at chiropractic appointments; 2) inability to read or speak English fluently; 3) concurrent rheumatic disease (except osteoarthritis; and 4) newly prescribed medication (less than 8 weeks), including NSAIDs, hypnotics and/or antidepressants. For ethical reasons, patients were allowed to take their prescribed medications (of > 8 weeks standing) during the study period.
Recruitment/selection of patients	Patients currently attending a university-based rheumatology clinic were telephoned by the physician to invite their participation in the trial.
Age, gender and ethnicity	Age - Mean (SD): Waiting list group 48.78 (7.69) ; Treatment group 49.1 (10.1). Gender (M:F): Not stated. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: No 3. Chronic visceral pain: No 4. Chronic widespread pain: Yes 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: No 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Extra comments	Years diagnosed, mean (SD): Waiting list group 3.67 (3.2) Treatment group 2.00 (1.76)
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Manual therapy - Mixed modality manual therapy. Chiropractic treatment was administered three to five times a week for 4 weeks. The treatment consisted of the following: Soft tissue massage: Soft tissue massage using a counter-irritant DEEP COLD or Glenalgesic Cream was performed over the involved hypertonic musculature. The most commonly involved muscles include: scalenes, posterior cervical, trapezius and lumbar paraspinal muscles. Soft tissue stretching: Passive assisted stretching and Fluorimethane spray and stretch techniques were done on the following muscles, as indicated: scalenes, posterior cervical muscles, quadratus lumborum, and lumbar

	and mid-thoracic paraspinals. In particular, Fluorimethane spray was used over the scalene muscles for the first three to six treatments. Spinal manipulation: Manipulation of the spinal joints was graded in velocity and amplitude. Initially, the velocity was slower and amplitude minimal to avoid aggravation of myofascial tissues. Indication for a manipulation was determined by a "hard-end" feel. Education: The patients were educated as to aggravating factors (i.e. cold excessive exertion, alcohol, caffeine, repetitive strain, etc.) proper sleep habits, good body mechanics for daily activities, natural history, origin and mechanism of their symptoms and prognosis. Each patient was treated individually so that each treatment regime was not identical. Duration 4 weeks. Concurrent medication/care: For ethical reasons, patients were allowed to take their prescribed medications (of > 8 weeks standing) during the study period. Indirectness: No indirectness (n=11) Intervention 2: Usual care. This group was a 'waiting list' control. Outcome measures were assessed at the end of the four weeks. However, after assessments had been made, they were also treated with the chiropractic program (for ethical reasons). Duration 4 weeks. Concurrent medication/care: For ethical reasons, patients were allowed to take their prescribed medications (of > 8 weeks standing) during the study period. Indirectness: No indirectness
Funding	Other (Funding was provided by Canadian Memorial Chiropractic College and North York Rehabilitation Center.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MODALITY MANUAL THERAPY versus USUAL CARE

Protocol outcome 1: Pain reduction
- Actual outcome: Pain rated on Visual Analogue Scale (VAS) at Post-treatment (4 weeks); Group 1: mean -17.3 (SD 30.55); n=10, Group 2: mean 4 (SD 18.76); n=9; VAS 0-100 Top=High is good outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Difference in baseline for years diagnosed and years of symptoms of fibromyalgia; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: Moved away (1), too far to travel (1)

Protocol outcome 2: Physical function
- Actual outcome: Oswestry Disability Index (ODI) at Post-treatment (4 weeks); Group 1: mean 2.3 (SD 12.38); n=10, Group 2: mean -0.11 (SD 14.22); n=9; Oswestry Disability Index 0-100 Top=High is poor outcome; Comments: Baseline values not reported.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Difference in baseline for years diagnosed and years of symptoms of fibromyalgia; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: Moved away (1), too far to travel (1)

Protocol outcome 3: Discontinuation

- Actual outcome: Drop out at Post-treatment (4 weeks); Group 1: 0/10, Group 2: 2/9; Comments: In usual care group two people dropped out from the protocol and were not assessed for outcome. One participant moved away during the intervention period and one decided it was too far to travel. Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Difference in baseline for years diagnosed and years of symptoms of fibromyalgia; Group 1 Number missing; Group 2 Number missing	
Protocol outcomes not reported by the study	Health related quality of life ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Brattberg 1999[39]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Sweden; Setting: not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 weeks + 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall: NA
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 48 (12.4) years. Gender (M:F): not reported. Ethnicity: not reported
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: No 3. Chronic visceral pain: No 4. Chronic widespread pain: Yes 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=27) Intervention 1: Manual therapy - Soft tissue technique. Connective tissue massage - 15 sessions over 10 weeks led by massage therapists - programme included massage of the pelvic area, back area, shoulder area, abdomen, legs and site of the pain; breathing exercises aiming to increase mobility of the diaphragm and recommendation to perform neck, low back and breathing exercises at home. Duration 10 weeks. Concurrent medication/care: 31% of all participants were taking analgesics, 19% were taking sedatives, 23% were taking hypnotics, 45% were taking antidepressants. Indirectness: No indirectness; Indirectness comment: NA (n=25) Intervention 2: Usual care. Reference group - study split in to two stages. In the first stage participants in the reference group received no treatment, in the second stage participants in the reference group participated in a group discussion once a week. No differences in outcomes were found between the two reference groups, so results were combined. Duration 10 weeks. Concurrent medication/care: 31% of all participants were taking analgesics, 19% were taking sedatives, 23% were taking hypnotics, 45% were taking antidepressants. Indirectness: Serious indirectness; Indirectness comment: half of the reference

	group participated in weekly group discussions - more than usual care
Funding	Other (supported by the Swedish Rheumatism Association)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus USUAL CARE

Protocol outcome 1: Pain reduction
- Actual outcome: Average pain during the previous week (VAS) at 10 weeks ; Group 1: mean 58.79 (SD 22.18); n=23, Group 2: mean 64.62 (SD 19.4); n=25; visual analogue scale 0-100 Top=High is poor outcome; Comments: Baseline values: soft tissue technique 66.46 (22.47), reference group 69.63 (19.92)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline group demographics not reported, outcome measures only; Group 1 Number missing: 4, Reason: not reported ; Group 2 Number missing: 0, Reason: not reported

Protocol outcome 2: Health related quality of life
- Actual outcome: Fibrositis Impact Questionnaire at 10 weeks ; Group 1: mean 52.09 (SD 16.02); n=23, Group 2: mean 64.86 (SD 16.33); n=25; Fibrositis Impact Questionnaire 0-100 Top=High is poor outcome; Comments: Baseline values: soft tissue technique 62.85 (15.91), reference group 67.65 (10.72)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline group demographics not reported, outcome measures only; Group 1 Number missing: 4, Reason: not reported ; Group 2 Number missing: 0, Reason: not reported

Protocol outcome 3: Physical function
- Actual outcome: Disability Rating Index at 10 weeks ; Group 1: mean 56.83 (SD 17.49); n=23, Group 2: mean 64 (SD 17.46); n=25; Disability Rating Index 0-100 Top=High is poor outcome; Comments: Baseline values: soft tissue technique 61.52 (14.77), reference group 66.8 (14.55)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline group demographics not reported, outcome measures only; Group 1 Number missing: 4, Reason: not reported ; Group 2 Number missing: 0, Reason: not reported

Protocol outcome 4: Psychological distress
- Actual outcome: Hospital Anxiety and Depression Scale - anxiety at 10 weeks ; Group 1: mean 7.26 (SD 4.23); n=23, Group 2: mean 9.08 (SD 4.29); n=25; HADS-anxiety 0-21 Top=High is poor outcome; Comments: Baseline values: soft tissue technique 9.39 (4.01), reference group 8.84 (4.14)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline group demographics not reported, outcome measures only; Group 1 Number missing: 4, Reason: not reported ; Group 2 Number missing: 0, Reason: not reported
- Actual outcome: Hospital Anxiety and Depression Scale - depression at 10 weeks ; Group 1: mean 6.24 (SD 4.67); n=23, Group 2: mean 8.64 (SD 4); n=25; HADS - depression 0-21 Top=High is poor outcome; Comments: Baseline values: soft tissue technique 8.65 (3.46), reference group 8.28 (4.94)
Risk of bias: All domain - ; Indirectness of outcome: No indirectness, Comments: NA

Protocol outcome 5: Sleep - Actual outcome: Sleep disturbance at 10 weeks ; Group 1: mean 3.27 (SD 0.73); n=23, Group 2: mean 3.62 (SD 0.69); n=25; Sleep disturbance (mean value for 10 questions about sleep) 0-5 Top=High is poor outcome; Comments: Baseline values: soft tissue technique 3.42 (0.57), reference group 3.63 (0.68) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline group demographics not reported, outcome measures only; Group 1 Number missing: 4, Reason: not reported ; Group 2 Number missing: 0, Reason: not reported Protocol outcome 6: Discontinuation - Actual outcome: Drop out at 10 weeks ; Group 1: 3/27, Group 2: 1/25; Comments: Overall reasons for drop out reported only (not per group): 1 due to heart disease, 2 due to lack of time, 1 due to traveling abroad. Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline group demographics not reported, outcome measures only; Group 1 Number missing; Group 2 Number missing	
Protocol outcomes not reported by the study	Pain interference ; Pain self-efficacy ; Use of healthcare services

Study	Campa-moran 2015[50]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=36)
Countries and setting	Conducted in Spain; Setting: not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 days + 1 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: In order to meet the criteria to participate in the study, patients had to pass an initial physical examination performed by a single investigator to rule out the presence of nerve root compression.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were selected if they met all of the following criteria: (a) bilateral pain involving the upper trapezius and elevator muscle of the scapula; (b) a duration of pain of at least 3 months; (c) a pain intensity corresponding to at least 20mm on a 100mm visual analogue scale (VAS); (d) neck pain with symptoms provoked by either neck postures or neck movement; (e) pain localized at least in the cervical and occipital regions but not in the orofacial region; (f) neck disability index (NDI) greater than or equal to 15 points; (g) restricted cervical range of movements (flexion, extension, rotation, and side-bending); (h) presence of bilateral MTrPs in upper trapezius and levator scapulae muscles. MTrPs were diagnosed according to the following criteria: (1) presence of a palpable taut band in skeletal muscle, (2) presence of a hypersensitive tender spot within this taut band, and (3) reproduction of referred pain in response to MTrP compression.
Exclusion criteria	Patients were excluded if they presented any signs, symptoms, or history of the following diseases: (a) orofacial pain and temporomandibular disorders according to the Research Diagnostic Criteria of Temporomandibular Disorders (RDC/TMD); (b) a history of traumatic injuries (e.g., contusion, fracture, and whiplash injury); (c) systemic diseases such as fibromyalgia, systemic erythematous lupus, and psoriatic arthritis; (d) neurologic disorders (e.g.,trigeminal neuralgia or occipital neuralgia); (e) concomitant medical diagnosis of any primary headache (tension type or migraine); (f) unilateral neck pain; (g) cervical spine surgery; (h) clinical diagnosis of cervical radiculopathy ormyelopathy; (i) needle phobia; (j) history of previous physical therapy intervention for the cervical region.
Recruitment/selection of patients	Participants were recruited from the PublicValleagudo Primary Health Care Center in Coslada, Madrid, Spain. Patients with cervical pain of muscular origin were referred and screened for possible eligibility criteria.
Age, gender and ethnicity	Age - Mean (SD): Dry needling group 53.9 (12.7); Soft tissue group 45.8 (15.4); Orthopedic therapy group 48.7 (10.2). Gender (M:F): 7 male / 29 female. Ethnicity: Not stated.

Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Acupuncture/dry needling. DN-S group received two treatments of bilateral dry needling on levator scapulae and upper trapezius muscles and a passive stretching technique. The needles used were 0.26 × 25mm. The technique began with palpation of the active MTrP localizing the more sensitive taught band of the muscle. The needle was inserted in the direction of the taught band and perpendicular to the skin and was directed to the muscle MTrP until a first local twitch response was provoked. Then, the needle was inserted and withdrawn; the local twitch response was perceived by the therapist as a transient and involuntary contraction of the taut band. The needle insertions were repeated to achieve at least three local twitch responses. Then, the needle was withdrawn. The needling procedure at each MTrP lasted about 2 minutes. Once the needle was withdrawn, firm compression was exerted on the insertion site for 40 seconds to avoid excessive bleeding. Following the needling procedure, a passive stretching to the levator scapulae and trapezius muscles was applied bilaterally for 20 seconds to each muscle. Duration 2 days (2 sessions). Concurrent medication/care: Not stated. Indirectness: No indirectness (n=12) Intervention 2: Manual therapy - Soft tissue technique. These patients received a bilateral osteopathic manual therapy treatment based on the ischemic compression technique over both the levator scapulae and upper trapezius muscles, but also a dynamic soft tissue mobilisation (DSTM) was applied on the upper trapezius for four minutes. For the ischemic compression technique, the physiotherapist (PT) applied gradually increasing pressure to the MTrP until the patient felt the sensation of pressure changed into pain; at that time the pressure was maintained until the discomfort eased, at which moment the pressure was increased until discomfort was again perceived by the patient. This process was repeated for 90 seconds while the patient was lying prone. The DSTM are a group of techniques used to treat the muscle, a direct stimulus over a specific region of the muscle (pressure, gliding pressure, etc.) added to stretching of the muscle or a mobilisation of the closest joint or both together. For the soft tissue group, a DSTM over the trapezius muscle was used. The patient was in lateral decubitus; the PT positioned one hand over the acromion and the other hand at the distal part of the upper trapezius. The technique consisted of performing a circular movement of the scapular belt while a slow gliding pressure was applied over the trapezius muscle in the direction to the occipital bone while the muscle was in a relaxed position. When the shoulder was depressed and therefore the muscle was stretched, nothing was performed over the muscle but the stretching itself. The technique was applied bilaterally for two minutes. Duration 2 days (2 sessions). Concurrent medication/care: Not stated. Indirectness: No indirectness

	(n=12) Intervention 3: Manual therapy - Manipulation/mobilisation. The mobilisation group received an osteopathic manual therapy protocol with a neural/joint approach, with three techniques: (1) anterior-posterior upper cervical mobilisation (APUCM) with wedge (four min); (2) the cervical lateral glide mobilisation technique at C4 and C5 (two min each side); and (3) neural thoracic mobilisation with wedge (four min). (1) APUCM: with the patient lying supine with a neutral position of the cervical spine, the wedge was positioned under the C2 spinous process. The PT held the occipital region of the patient with both hands to stabilize and maintain the position of the upper cervical structures, while with the anterior part of his shoulder applying a posteriorly directed force on the frontal region of the patient (anterior to posterior force). The mobilisation was applied at a slow rate of one oscillation per two seconds (0.5Hz) controlled with a digital metronome MA-30 (Korg Inc., Japan). The total time of mobilisation was four minutes, applied for two intervals of two minutes each, with 30 seconds rest in between. (2) Cervical lateral glide mobilisation technique: with the patient in a supine position, the PT cradled the head and neck of the patient and, including the levels to be treated (C4-C5), performed a lateral translatory movement while minimizing gross cervical side flexion or rotation, spending two min at each point and side and a total of eight min. (3) Neural thoracic mobilisation: patient was lying supine, with both knees in flexion and one leg crossed over the other, maintaining the knees together. A wedge is placed under the patient's back, with the upper side at T4-T5 level. Te PT holds the head with the forearm in a craniocervical flexion and submaximal cervical flexion; the hand is placed under the spine at the mobilisation level, to ensure the vertebrae are mobilizing. A towel is placed over the sternum of the patient and the other hand of the PT is placed over the towel to exert an anterior-posterior pressure. This is a dynamic technique; the patient is asked to extend the crossed leg without losing the knee-knee contact, and when the patient again flexed the knee, the PT applied the pressure over the sternum. Duration 2 days (2 sessions). Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated (The authors declare that there is no conflict of interests regarding the publication of this paper.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus ACUPUNCTURE/DRY NEEDLING

Protocol outcome 1: Pain reduction
- Actual outcome: Pain on VAS at 1 week follow-up (9 days); Group 1: mean 34.3 (SD 14.79); n=12, Group 2: mean 13.3 (SD 14.79); n=12; Visual Analogue Scale 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Manipulation group 42.1 (16.3) Soft tissue group 50.2 (17.7) Dry needling group 33.8 (11.7)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details:; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Physical function

- Actual outcome: Neck Disability Index (NDI) at 1 week follow-up (9 days); Group 1: mean 15.2 (SD 5.51); n=12, Group 2: mean 12.2 (SD 5.35); n=12; Neck Disability Index 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Soft tissue group 17.4 (4.8) Dry needling group 18 (5.4)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 3: Psychological distress
- Actual outcome: Pain Catastrophizing Scale (PCS) at 1 week follow-up (9 days); Group 1: mean 16.4 (SD 4.56); n=12, Group 2: mean 18.2 (SD 0.81); n=12; Pain Catastrophizing Scale (PCS) 0-52 Top=High is poor outcome; Comments: Baselines, mean (SD): Soft tissue group 17.5 (4.5) Dry needling group 19.2 (6.4)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANIPULATION/MOBILISATION versus ACUPUNCTURE/DRY NEEDLING

Protocol outcome 1: Pain reduction
- Actual outcome: Pain on VAS at 1 week follow-up (9 days); Group 1: mean 9.4 (SD 14.79); n=12, Group 2: mean 13.3 (SD 14.79); n=12; Visual Analogue Scale 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Mobilisation group 42.1 (16.3) Dry needling group 33.8 (11.7)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details:; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Physical function

- Actual outcome: Neck Disability Index (NDI) at 1 week follow-up (9 days); Group 1: mean 10 (SD 5.51); n=12, Group 2: mean 12.2 (SD 5.35); n=12; Neck Disability Index 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Manipulation group 18.5 (3.2) Dry needling group 18 (5.4)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 3: Psychological distress
- Actual outcome: Pain Catastrophizing Scale (PCS) at 1 week follow-up (9 days); Group 1: mean 13.1 (SD 4.72); n=12, Group 2: mean 18.2 (SD 0.81); n=12; Pain Catastrophizing Scale (PCS) 0-52 Top=High is poor outcome; Comments: Baselines, mean (SD): Manipulation group 18.3 (4.2) Dry needling group 19.2 (6.4)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANIPULATION/MOBILISATION versus SOFT TISSUE TECHNIQUE

Protocol outcome 1: Pain reduction

- Actual outcome: Pain on VAS at 1 week follow-up (9 days); Group 1: mean 9.4 (SD 14.79); n=12, Group 2: mean 34.3 (SD 14.79); n=12; Visual Analogue Scale 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Manipulation group 42.1 (16.3) Soft tissue group 50.2 (17.7) Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details:; Group 1 Number missing; Group 2 Number missing Protocol outcome 2: Physical function - Actual outcome: Neck Disability Index (NDI) at 1 week follow-up (9 days); Group 1: mean 10 (SD 5.51); n=12, Group 2: mean 15.2 (SD 5.51); n=12; Neck Disability Index 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Manipulation group 18.5 (3.2) Soft tissue group 17.4 (4.8) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing Protocol outcome 3: Psychological distress - Actual outcome: Pain Catastrophizing Scale (PCS) at 1 week follow-up (9 days); Group 1: mean 13.1 (SD 4.72); n=12, Group 2: mean 16.4 (SD 4.56); n=12; Pain Catastrophizing Scale (PCS) 0-52 Top=High is poor outcome; Comments: Baselines, mean (SD): Manipulation group 18.3 (4.2) Soft tissue group 17.5 (4.5) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing	
Protocol outcomes not reported by the study	Health related quality of life ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Ceca 2017[60]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in Spain; Setting: Sports centers in Valencia, Spain.
Line of therapy	Unclear
Duration of study	Intervention time: 20 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fibromyalgia syndrome diagnosed according to the diagnostic criteria proposed by the American College of Rheumatology.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People diagnosed with fibromyalgia syndrome, according to the diagnostic criteria proposed by the American College of Rheumatology. Inclusion criteria were: being over 18 years of age, having a diagnosis of fibromyalgia syndrome and having signed the informed consent.
Exclusion criteria	Exclusion criteria were: having a diagnosis of heart, kidney or liver failure, respiratory problems that could limit the application of the program, a cardiovascular event during the last year, not agreeing to follow the proposed intervention program, and not being considered outliers (individual values greater than the mean plus 2 SDs).
Age, gender and ethnicity	Age - Mean (SD): Not stated. Gender (M:F): 4 male / 39 female (analysed). Ethnicity: White.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: No 3. Chronic visceral pain: No 4. Chronic widespread pain: Yes 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Manual therapy - Soft tissue technique. Self-myofascial release program: participants in the intervention group followed a 20-week self-myofascial release program consisting of two 50-minute sessions per week. The sessions were structured in three parts. First, the participants performed mobility exercises involving major muscle groups for ten minutes. They then continued with thirty minutes of self-myofascial release exercises using different materials according to the intensity of pressure required for each muscle group at each stage in the program. The main part of all sessions ended with a self-myofascial release exercise for the trapezius muscle. Lastly, the session ended with ten minutes of static stretching exercises. A single set of 10 repetitions (45-60 seconds) was performed for each exercise. Of the two scheduled weekly sessions, one of them worked on the muscles of the upper body, while the

	exercises in the other session focused on the muscle groups of the lower body. These exercises were always led by a specialist in physical activity whose example the subjects copied. Throughout the program the pressure exerted gradually increased in intensity. This progression was based on three premises: hardness of the material, body weight resting on the material and size of the contact surface with the material. In relation to the hardness of the material and the size of the contact surface, five tools were used during the sessions of the program, ordered from least to greatest pressure exerted: large foam balls, small foam balls, spiky rubber balls, foam rollers and tennis balls. All the required material was administered by the research group. Three types of exercises were prepared for different areas of application based on the body weight resting on the material, ordered from lowest to highest intensity: hand exercises, in which the participants applied pressure to the material with their hand in order to massage their muscles; standing exercises, in which the participants applied pressure to the material, which in turn was situated between the participants body and the wall; floor exercises, in which the subject rested all their body weight on the material, which was situated between the participants body and the floor. Duration 20 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=33) Intervention 2: Usual care. The control group received no treatment. No further details given. Duration 20 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Other (Supported by Decathlon San Antonio (Valencia, Spain), which donated some of the equipment used in the study, and has been made possible thanks to funding from the Catholic University of Valencia "San Vicente Martir" through the grants for hiring trainee research personnel (2013). The study stated no financial benefit for the authors, and that it represents results of original work that have not been published elsewhere in any form.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus USUAL CARE

Protocol outcome 1: Health related quality of life
- Actual outcome: Fibromyalgia Impact Questionnaire, Spanish version (FIQ-S) - overall score at Post-treatment; Group 1: mean 28.99 (SD 11); n=23, Group 2: mean 35.22 (SD 7.41); n=20; Fibromyalgia Impact Questionnaire - Spanish (FIQ-S) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Intervention group 38.92 (5.78) Control group 35.66 (6.01)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: lost to follow-up due to new job, surgical intervention or timetable problems; Group 2 Number missing: 13, Reason: lost to follow-up due to non-attendance

Protocol outcome 2: Discontinuation
- Actual outcome: Drop out at Post-treatment; Group 1: 0/33, Group 2: 0/33
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing

Protocol outcomes not reported by the study	Pain reduction ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	**Fitzgerald 2012**[104]

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=81)
Countries and setting	Conducted in USA; Setting: MPT or GTM was performed at 11 clinical centers located in North America.
Line of therapy	Unclear
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis of IC/PBS (interstitial cystitis/painful bladder syndrome)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Female patients were eligible for inclusion if they had a clinical diagnosis of IC/PBS, and recorded ratings for bladder pain, frequency, and urgency each at a usual level of at least 3 on a 0-10 scale, present for at least three months but not longer than 3 years. An additional eligibility requirement was the finding of pelvic floor tenderness during vaginal examination by the study physician, confirmed by the study physical therapist.
Exclusion criteria	Women were excluded if they had not previously undergone at least one course of a standard therapy for IC/PBS or if they had previously received treatment with pelvic floor MPT.
Recruitment/selection of patients	Recruited women with IC/PBS with demonstrable pelvic floor tenderness on physical examination and a limitation of no more than 3 years symptom duration.
Age, gender and ethnicity	Age - Mean (SD): Soft tissue group 43.0 (12.9); Manipulation group 43.1 (15.1). Gender (M:F): All women (81). Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: No 3. Chronic visceral pain: Yes 4. Chronic widespread pain: No 5. Cognitive impairment: No 6. Complex regional pain syndrome: No 7. First language not English: No 8. Homeless: No 9. Learning difficulties: No 10. Sensory impairment: No

Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Manual therapy - Soft tissue technique. Global therapeutic massage (GTM). The GTM treatment followed a traditional full-body Western massage program. Physical therapists from each site were centrally trained and certified in the performance of both interventions to standardize treatment. Subjects received up to ten, 60-minute treatment sessions over a 12-week time period. Duration Up to ten 60 minute sessions over 12 weeks. Concurrent medication/care: None stated. Indirectness: No indirectness (n=39) Intervention 2: Manual therapy - Manipulation/mobilisation. Myofascial physical therapy (MPT) Those randomized to MPT received targeted internal and external tissue manipulation focusing on the muscles and connective tissues of the pelvic floor, hip girdle, and abdomen. The MPT methodology has been described in detail previously. Physical therapists from each site were centrally trained and certified in the performance of both interventions to standardize treatment. Subjects received up to ten, 60-minute treatment sessions over a 12-week time period. Duration Up to ten 60 minute sessions over 12 weeks. Concurrent medication/care: None stated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus MANIPULATION/MOBILISATION

Protocol outcome 1: Pain reduction
- Actual outcome: Bladder pain on VAS (Likert scale) at 12 weeks (post-treatment); Group 1: mean 4.3 (SD 2.3); n=40, Group 2: mean 3.8 (SD 2.3); n=38; VAS (Likert scale) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Soft tissue group 5.8 (1.7) Manipulation group 6.1 (1.7)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Personal reasons or dissatisfaction with treatment (unclear which); Group 2 Number missing: 1, Reason: Personal reasons or dissatisfaction with treatment (unclear which)

Protocol outcome 2: Health related quality of life
- Actual outcome: SF-12 MCS (mental component summary) at 12 weeks (post-treatment); Group 1: mean 49.3 (SD 8.5); n=40, Group 2: mean 45 (SD 10.8); n=38; SF-12 MCS 0-100 Top=High is good outcome; Comments: Baselines, mean (SD): Soft tissue group 45.8 (8.8) Manipulation group 40.1 (8.9)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Personal reasons or dissatisfaction with treatment (unclear which); Group 2 Number missing: 1, Reason: Personal reasons or dissatisfaction with treatment (unclear which)
- Actual outcome: SF-12 PCS (physical component summary) at 12 weeks (post-treatment); Group 1: mean 46 (SD 10.5); n=40, Group 2: mean 45.6 (SD 9.4); n=38; SF-12 PCS 0-100 Top=High is good outcome; Comments: Baselines, mean (SD): Soft tissue group 45.4 (10) Manipulation group 41.5 (10)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Personal reasons or dissatisfaction with treatment (unclear which); Group 2 Number missing: 1, Reason: Personal reasons or dissatisfaction with treatment (unclear which) Protocol outcome 3: Discontinuation - Actual outcome: Dropout/withdrawal before end of treatment at 12 weeks (post-treatment); Group 1: 2/42, Group 2: 1/39; Comments: Two participants withdrew due to "personal constraints", one withdrew due to being "dissatisfied with treatment". It is unclear which group had the dropout due to dissatisfaction. Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Lin 2013[174]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in China; Setting: not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 24 days + 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Individuals were diagnosed with mechanical neck pain by a clinical doctor according to the diagnosis criteria.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis criteria: 1) neck pain without neurologic or vascular deficit, 2) restriction of movement of a motion segment identified by static or motion palpation, 3) possible discomfort with joint challenge/pressure, 4) abnormal changes of cervical curve and alignment in radiological test. Inclusion criteria: a diagnosis of mechanical neck pain, more than three month history of neck pain, age between eighteen and sixty-five and being able to read Chinese.
Exclusion criteria	Neck pain referred from peripheral joints or viscera, rheumatic fibromyalgia and neurasthenia were excluded. Other exclusion criteria were: 1) contraindications to manipulation (e.g. infection, malignancy, osteoporosis, spinal fracture, inflammatory conditions, nerve root involvement, etc), 2) history of whiplash or surgery to the neck, 3) congenital abnormality of the cervical spine, 4) diagnosis of cervical radiculopathy or myelopathy, 5) cardiac disease requiring medical treatment, 6) having received Long's manipulation or other bone-setting treatment in the past 3 months.
Recruitment/selection of patients	Patients were recruited in an outpatient clinic of the first affiliated Hospital of the Guangzhou Medical College from February 2011 to March 2012.
Age, gender and ethnicity	Age - Mean (SD): Manipulation group 38.94 (11.71) ; Massage group 40.90 (11.80). Gender (M:F): 17 male / 46 female. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Manual therapy - Mixed modality manual therapy. Long's manipulation was performed through the following procedure: 1) Relaxation step, in which the subject lay supine or on the side with the neck and head fully supported by a

	pillow. The manual therapist massaged the soft tissue that covers 3 vertebras up and down from the targeted level to release the tension or spasm. Massage techniques, such as kneading, pinching and plucking, were selected accordingly. 2) Manipulation step: the subject lay on their side while the therapist placed one hand under the patient's face to gently hold the head. The other hand stabilised the head and neck with one finger palpating the tension of the tissues. The therapist gently flexed the patient's neck until the tension was palpated at the targeted level, and then rotated the neck around the axis of the cervical spine to endpoint. A high velocity low amplitude technique was applied to the joint if no discomfort was reported by the patient. 3) Reinforcing step: provocative massage techniques, including pinching, plucking, clapping and acupressure, were performed to improve sensation in the neck area or upper limb accordingly. 4) Painful region massage step: gentle massage techniques, such as stroking, rubbing and shaking, were applied to the affected region. Each patient received eight 20-minute sessions of assigned therapy. They were asked to attend the treatment every three days. The therapy was performed by a therapist who had at least 5 years' experience of practice of Long's manipulation for neck pain. The manual therapist varied the force of the therapy according to the patient's response. Duration 8 sessions over 24 days. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=30) Intervention 2: Manual therapy - Soft tissue technique. Patients in the control group received only the traditional Chinese massage techniques from the Long's manipulation program. The traditional Chinese massage was performed according to steps 1, 3 and 4 of the Long's manipulation treatment. Each patient received eight 20-minute sessions of assigned therapy. They were asked to attend the treatment every three days. The therapy was performed by a therapist who had at least 5 years' experience of practice of massage for neck pain. The manual therapist varied the force of the therapy according to the patient's response. Duration 8 sessions over 24 days. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MODALITY MANUAL THERAPY versus SOFT TISSUE TECHNIQUE

Protocol outcome 1: Pain reduction
- Actual outcome: Numeric pain rating scale (NPRS) at Post-treatment (24 days); Group 1: mean 2.06 (SD 1.65); n=33, Group 2: mean 4.04 (SD 1.59); n=30; Numeric pain rating scale (NPRS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Long's manipulation group 5.79 (1.96) Massage group 5.63 (1.90)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Not enough time to attend (2); Group 2 Number missing: 4, Reason: Not enough time to attend (2), concurrent treatment (1), worsening of symptoms (1)

- Actual outcome: Numeric pain rating scale (NPRS) at 3 month follow-up; Group 1: mean 2.07 (SD 1.44); n=33, Group 2: mean 4.54 (SD 2.26); n=30; Numeric pain rating scale (NPRS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Long's manipulation group 5.79 (1.96) Massage group 5.63 (1.90) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Not enough time to attend (2), concurrent treatment (2); Group 2 Number missing: 13, Reason: Not enough time to attend (5), concurrent treatment (8) Protocol outcome 2: Discontinuation - Actual outcome: Drop out at Post-treatment (24 days); Group 1: 2/33, Group 2: 4/30; Comments: Reasons for drop out: Intervention: Not enough time to attend (2) Control: Not enough time to attend (2), concurrent treatment (1), worsening of symptoms (1) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Not enough time to attend (2); Group 2 Number missing: 4, Reason: Not enough time to attend (2), concurrent treatment (1), worsening of symptoms (1)	
Protocol outcomes not reported by the study	Health related quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Llamas-ramos 2014[176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=94)
Countries and setting	Conducted in Spain; Setting: Not stated.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks + 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were examined for the presence of active TrPsin the upper trapezius muscle by a clinician with more than 6 years of experience in the management of TrPs.
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	Mechanical neck pain was defined as neck and shoulder pain with symptoms provoked by neck postures, neck movement, or palpation of the cervical muscles. Participants were screened for signs of vertebrobasilar insufficiency (eg, nystagmus, gait disturbances, or Horner's syndrome) and underwent manual screening for upper cervical spine ligamentous instability (Sharp-Purser test, alar ligament stress test, and transverse ligament tests).
Exclusion criteria	Participants were excluded if they exhibited any of the following criteria:(1) whiplash injury, (2) previous cervical surgery, (3) cervical radiculopathy or myelopathy, (4) diagnosis of fibromyalgia, (5) any physical therapy intervention in the previous year, (6) fear of needles, or(7) any contraindication for dry needling (eg, anticoagulants or psychiatric disorders).
Recruitment/selection of patients	Consecutive patients with chronic idiopathic mechanical neck pain were referred by their physician.
Age, gender and ethnicity	Age - Mean (SD): Manual therapy group 31 (2) ; Dry needling group 31 (3). Gender (M:F): 32 male / 62 female. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Extra comments	The diagnosis of a TrP was determined by the presence of all of the following: (1) a hypersensitive spot in a palpable taut band, (2) palpable or visible local twitch on pincer palpation, and (3) reproduction of referred pain elicited by palpation of the sensitive spot. The TrPs were considered active when the referred pain elicited by palpation reproduced the neck symptoms and the patients recognized the pain as their familiar symptoms.
Indirectness of population	No indirectness

Interventions	(n=47) Intervention 1: Manual therapy - Soft tissue technique. Pressure release over the upper trapezius TrP was applied. Briefly, pressure was progressively increased over the TrP until a definite in-crease in tissue resistance (barrier) was perceived by the therapist. This pressure was maintained until the clinician sensed a relief of the taut band. At that time, the pressure was increased again until the clinician felt the next increase in tissue resistance. This process was repeated 3 times at each session. Patients also received a stretching intervention of the taut-band muscle fibers. Both thumbs of the therapist were placed over the taut band, above and below the TrP. The therapist applied moderate, slow pressure over the TrP, sliding the fingers in opposite directions. Trigger point manual therapy was applied slowly, without inducing pain. Passive stretching of the upper trapezius muscle was also performed for 45 seconds. First session at day 1 after baseline outcomes were collected. The patients returned 1 week later for the second session. Treatment was applied to the symptomatic side of the neck. Duration 2 weeks (2 sessions). Concurrent medication/care: None stated. Indirectness: No indirectness (n=47) Intervention 2: Acupuncture/dry needling. The clinician applied trigger point dry needling to the upper trapezius muscle. The trigger point needling was performed with disposable stainless-steel needles (0.3 × 30 mm; Novasan, S.A.,Madrid, Spain) inserted into the skin over the trigger point (TrP) area, using the fast-in and fast-out technique. Once the TrP was located with pincer palpation in the upper trapezius, the over-lying skin was cleaned with alcohol. The needle was inserted so as to penetrate the skin 10 to 15 mm into the TrP until a local twitch response was obtained. Once the first local twitch response was obtained, the needle was moved up and down (2- to 3-mm vertical motions with no rotations) at approximately 1 Hz for 25 to 30 seconds. First session at day 1 after baseline outcomes were collected. The patients returned 1 week later for the second session. Treatment was applied to the symptomatic side of the neck. Duration 2 weeks (2 sessions). Concurrent medication/care: None stated. Indirectness: No indirectness
Funding	Other (The authors certify that they have no affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the article.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus ACUPUNCTURE/DRY NEEDLING

Protocol outcome 1: Pain reduction
- Actual outcome: Pain intensity on numeric rating scale at 4 weeks; Group 1: mean 1 (SD 1.1); n=46, Group 2: mean 0.9 (SD 0.8); n=45; Numeric rating scale 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Manual therapy group 6.2 (1.3) Dry needling group 6.2 (1.0)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Participant moved; Group 2 Number missing: 2, Reason: No contact.

Protocol outcome 2: Discontinuation
- Actual outcome: Drop-out at 4 weeks; Group 1: 0/47, Group 2: 0/47

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Participant moved; Group 2 Number missing: 2, Reason: No contact.	
Protocol outcomes not reported by the study	Health related quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Madson 2010[179]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=23)
Countries and setting	Conducted in USA; Setting: Physical therapy practice of a tertiary care centre.
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: An initial evaluation was performed by 1 of 2 physical therapists to determine if prospective subjects met the study criteria. Patients were examined using standard physical therapy and manual medicine evaluation methods including neck and upper back postural assessment, neck and shoulder active range of motion, upper extremity manual muscle testing, tendon stretch reflexes, and light touch sensation.
Stratum	Overall: Because symptoms of cervical spine osteoarthritis have been reported to be more prominent after the age of 60, subjects were stratified by age (</=60, >60 years) to ensure a balanced distribution.
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	All subjects had neck pain of at least 12 weeks duration and were between the ages of 20 and 80 years old.
Exclusion criteria	Subjects with signs or symptoms of cervical radiculopathy, myelopathy, symptomatic shoulder pathology, fibromyalgia, generalized pain syndrome, or a history of cancer affecting the head or neck were excluded. In addition, subjects with a history of cervical spine surgery, motor vehicle accident within the past 3 years, or recent neck or shoulder trauma were also excluded.
Recruitment/selection of patients	Referred by physicians.
Age, gender and ethnicity	Age - Mean (SD): Mobilisation group 52.2 (14.0) ; Massage group 47.3 (15.3). Gender (M:F): 7 male / 16 female. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not stated / Unclear 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Manual therapy - Manipulation/mobilisation. Subjects received joint mobilisation (JM) to the cervical spine. Cervical spine mobilisation techniques were directed at segmental levels deemed restricted by the treating physical therapist on the day of treatment. Only low-grade (I, II, III, IV Matiland), non-thrust, oscillatory techniques were allowed. These could include transverse glides posterior/anterior glides and rotational techniques. Within these parameters, the choice of technique and number of repetitions was left to the treating therapist's discretion.

	Subjects were treated 2 or 3 times per week for 4 weeks (8-12 total sessions). Whether subjects received 2 or 3 treatments per week was solely based on their ability to attend treatment sessions. Therapist contact time was around 30 minutes per session in each group after the application of moist hot packs. All subjects received most heat packs to their neck and upper back for 20 to 30 minutes before mobilisation. In addition, all subjects were instructed in head, beck, and upper back posture education principles and taught cervical spine active range of motion exercises. Duration 4 weeks. Concurrent medication/care: Other therapeutic interventions and modalities were not allowed, but patients were allowed to continue taking prescribed pain medications. Indirectness: No indirectness (n=12) Intervention 2: Manual therapy - Soft tissue technique. Subjects received sedative massage (SM) to the neck and upper back. Sedative massage included effluerage, stroking, and petrissage to the subject's neck and upper back musculature. Deep soft tissue, myofascial release, or craniosacral techniques were not allowed. Subjects were treated 2 or 3 times per week for 4 weeks (8-12 total sessions). Whether subjects received 2 or 3 treatments per week was solely based on their ability to attend treatment sessions. Therapist contact time was around 30 minutes per session in each group after the application of moist hot packs. All subjects received most heat packs to their neck and upper back for 20 to 30 minutes before mobilisation. In addition, all subjects were instructed in head, beck, and upper back posture education principles and taught cervical spine active range of motion exercises. Duration 4 weeks. Concurrent medication/care: Other therapeutic interventions and modalities were not allowed, but patients were allowed to continue taking prescribed pain medications. Indirectness: No indirectness
Funding	No funding (No funding sources or conflicts of interest were reported for this study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANIPULATION/MOBILISATION versus SOFT TISSUE TECHNIQUE

Protocol outcome 1: Pain reduction
- Actual outcome: Pain on visual analogue scale (VAS) at Post-treatment; Group 1: mean 16.45 (SD 13.69); n=11, Group 2: mean 20.91 (SD 20.46); n=12; Visual analogue scale (VAS) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Mobilisation group 40.91 (25.31) Massage group 29.42 (17.85)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in outcome at baseline; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Physical function
- Actual outcome: Neck Disability Index (NDI) at Post-treatment; Group 1: mean 5.64 (SD 3.61); n=11, Group 2: mean 8.08 (SD 5.28); n=12; Neck Disability Index (NDI) 0-50 Top=High is poor outcome; Comments: Baselines, mean (SD): Mobilisation group 13.54 (5.39) Massage group 12.75 (5.86)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 3: Discontinuation - Actual outcome: Discontinuation at Post treatment; Group 1: 0/11, Group 2: 0/12 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing	
Protocol outcomes not reported by the study	Health related quality of life ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Plews-ogan 2005[215]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in USA; Setting: not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 weeks + 4 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Assessment of pain sensation and unpleasantness was performed with 0 to 10 numeric rating scales obtained at baseline. A radio analogy was used to distinguish between pain sensation and unpleasantness with pain sensation the volume of the pain and unpleasantness how annoying the pain is. Participants reported average pain ratings over the previous week with 0= ‘‘none’’ and 10= ‘‘worst imaginable.’’ Global physical and mental health status was measured with the SF-12.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with musculoskeletal pain for greater than 3 months
Exclusion criteria	Exclusion criteria included: prisoner status, cognitive impairment, lack of reliable transportation, or being pregnant.
Recruitment/selection of patients	Patients were recruited with a flyer distributed during clinic visits from two general internal medicine practices at the University of Virginia.
Age, gender and ethnicity	Age - Mean (SD): 46.5. Gender (M:F): 7 male / 23 female. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: No 6. Complex regional pain syndrome: No 7. First language not English: Not stated / Unclear 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Extra comments	The sample size of 10 per group was established arbitrarily as a reasonable number to estimate the feasibility of a larger trial.
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Manual therapy - Soft tissue technique. One-hour massage sessions were given once per week for 8 weeks by 3 licensed massage therapists. Massage techniques were at the discretion of the therapists and included Swedish, deep-tissue, neuromuscular, and pressure-point techniques. We specifically excluded music, scented oils, and energy techniques such as Reiki or therapeutic touch. Duration 8 weeks. Concurrent medication/care: All participants continued their use of prescribed pain medication. (Report states that sixty percent of the recruited participants were taking at least 1 narcotic medication and 40% were taking only non-narcotic medications, but not a breakdown across groups.).

	Indirectness: No indirectness (n=10) Intervention 2: Usual care. Standard care at the 2 practices was to be seen by a primary care physician at least every 3 months with medication adjustments made as indicated. Duration 8 weeks. Concurrent medication/care: All participants continued their use of prescribed pain medication. (Report states that sixty percent of the recruited participants were taking at least 1 narcotic medication and 40% were taking only non-narcotic medications, but not a breakdown across groups). Indirectness: No indirectness
Funding	Other (Authors report no conflict of interest. Study was supported in part by Grant 1D12HP00040-03: Academic Administrative Units in Primary Care, Department of Health and Human Services and in part by the John W Kluge Foundation.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus USUAL CARE Protocol outcome 1: Pain reduction - Actual outcome: Pain unpleasantness on numeric rating scale at Post-treatment (8 weeks); Group 1: mean -2.9 (SD 2.9); n=9, Group 2: mean -0.13 (SD 2.4); n=8; Numeric rating scale 0-10 Top=High is poor outcome Risk of bias: All domain – Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline details not published; Group 1 Number missing: 1, Reason: Dropped out sooner after consent; Group 2 Number missing: 2, Reason: Dropped out sooner after consent. Protocol outcome 2: Health related quality of life - Actual outcome: SF-12 Mental health at Post-treatment (8 weeks); Group 1: mean 13.6 (SD 8.9); n=9, Group 2: mean 3.9 (SD 28); n=8; SF-12 Mental health 0-100 Top=High is good outcome Risk of bias: All domain – Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline details not published; Group 1 Number missing: 1, Reason: Dropped out sooner after consent; Group 2 Number missing: 2, Reason: Dropped out sooner after consent.	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Puntumetakul 2019[218]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Thailand
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: For study purposes, mechanical neck pain was defined as pain in the posterior neck or shoulder with mechanical characteristics, accompanied by symptoms provoked by sustained neck posture, neck movement, or palpation of the cervical musculature.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria were patients aged 18–59 years with chronic mechanical neck pain for ≥3 months, with a baseline VAS pain rating score of ≥3 prior to data collection. The participants were asked to complete a screening questionnaire to ensure that they met the inclusion criteria. Thereafter, they underwent a standard subjective and physical examination administered by an experienced physical therapist.
Exclusion criteria	The exclusion criteria were: 1) a diagnosis of cervical radiculopathy or myelopathy; 2) a history of whiplash injury; 3) a history of cervical surgery and/or thoracic surgery; 4) a history of cervical and/or thoracic injuries (including fracture or dislocation); 5) a diagnosis of fibromyalgia syndrome; 6) previous spinal manipulation within two months of participation in the present study; 7) serious spinal pathology (including spinal osteoporosis, spinal tuberculosis, and tumors); and 8) hypertension, heart disease, and meningitis.
Recruitment/selection of patients	Participants were recruited through advertising flyers that were posted within the local community area inviting participation in the research.
Age, gender and ethnicity	Age - Mean (SD): Overall: 23 (3.65) years. Manipulation group 23.27 (4.5). Mixed manual therapy group: 23.07 (2.71). Gender (M:F): 8 male, 22 female. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: No 6. Complex regional pain syndrome: No 7. First language not English: No 8. Homeless: No 9. Learning difficulties: No 10. Sensory impairment: No
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Manual therapy - Mixed modality manual therapy. Thoracic manipulation followed by the application of the Rungthip massage technique. Thoracic manipulation was performed at the same site and with the same protocol as the manipulation group, followed by a one-minute break, after which the Rungthip massage technique was administered. The latter was performed with the participants in the side-lying position, with 90 degrees of hip flexion and 90

	degrees of knee flexion. The therapist gently pressed her thumb along the treatment lines from the level of the inferior angle of the scapula to the lowest rib. Three repetitions were performed along each treatment line. Duration 3 weeks (6 sessions). Concurrent medication/care: Neck care education, including advice on how to adopt a neutral sitting posture and safe lifting posture, was given to all the study subjects. Indirectness: No indirectness (n=15) Intervention 2: Manual therapy - Manipulation/mobilisation. Thoracic manipulation. Thoracic manipulation was performed directly on both sides of the T6–T7 zygapophyseal joints of the control group participants at each treatment session. The participants were asked to lie in the prone position on the examination table and instructed to inhale and exhale deeply. During exhalation, the therapist performed thoracic manipulation (screw thrust technique) at the T6–T7 zygapophyseal joints, as described by Maitland et al). If a popping sound was not heard on the first attempt, the therapist repositioned the participant and performed a second manipulation. A maximum of two attempts was carried out within two minutes. Duration 3 weeks (6 sessions). Concurrent medication/care: Neck care education, including advice on how to adopt a neutral sitting posture and safe lifting posture, was given to all the study subjects. Indirectness: No indirectness
Funding	Other (Research Center of Back, Neck, Other Joint Pain, and Human Performance (BNOJPH))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MODALITY MANUAL THERAPY versus MANIPULATION/MOBILISATION Protocol outcome 1: Pain reduction - Actual outcome: Pain at rest on VAS at Post-treatment; Group 1: mean 9.67 (SD 6.52); n=15, Group 2: mean 20.71 (SD 12.37); n=15; Visual analogue scale (VAS) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Manual therapy group 42.33 (7.72) Manipulation group 45.29 (11.53) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health related quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Sherman 2014[245]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=228)
Countries and setting	Conducted in USA; Setting: single research clinic
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: in person examination
Stratum	Overall: NA
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Adults aged 20 to 64 years with chronic nonspecific neck pain lasting at least 3 months who were able and willing to attend treatments at our clinic and give informed consent
Exclusion criteria	individuals whose neck pain had a pathologically identifiable cause (e.g. vertebral fracture, metastatic cancer); was complex (e.g. cervical radiculopathy, recent automobile accident); was too mild, defined as scoring less than 4 on a pain intensity scale ranging from 0 to 10 and less than 5 on the Neck Disability Index (NDI) ranging from 0 to 50; those with potential contraindications for massage (e.g. hypersensitivity to touch); any massage within the last 3 months, massage for neck pain within the last year; inability to give informed consent or speak English; persons with medicolegal issues related to neck or back pain.
Recruitment/selection of patients	mailed invitations to Group Health members with neck pain–related visits to primary care clinicians, advertisements in the health plan's magazine, posters, a study website, neighbourhood blogs, and direct-mail postcards
Age, gender and ethnicity	Age - Mean (SD): control 44.4 (12.2), 1x60min/week 50.2 (10.9), 2x30min/week 42.3 (11.3), 2x60min/week 48.7 (11.5), 3x30min/week 45.7 (11.5), 3x60min/week 49 (9.9) years. Gender (M:F): 64/164. Ethnicity: White non-Hispanic: control 81.1%, 1x60min/week 78.9%, 2x30min/week 71.1%, 2x60min/week 84.2%, 3x30min/week 54.1%, 3x60min/week 76.3%
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not stated / Unclear 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=38) Intervention 1: Manual therapy - Soft tissue technique. 1 x 60 min/week massage - included range of motion assessment, hands-on check-in, massage applied directly to the neck, addressing compensatory

	patterns, and integration (reestablishment within a patient of being in a unified body after having received intensive isolated work). Therapists (8 licensed therapists with at least 5 years of experience) were given time limits for each part of the massage and permitted to use a broad range of massage techniques. No self-care recommendations were permitted. Duration 4 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA (n=38) Intervention 2: Manual therapy - Soft tissue technique. 2 x 30 min/week massage - included range of motion assessment, hands-on check-in, massage applied directly to the neck, addressing compensatory patterns, and integration (reestablishment within a patient of being in a unified body after having received intensive isolated work). Therapists (8 licensed therapists with at least 5 years of experience) were given time limits for each part of the massage and permitted to use a broad range of massage techniques. No self-care recommendations were permitted. Duration 4 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA (n=39) Intervention 3: Manual therapy - Soft tissue technique. 2 x 60 min/week massage - included range of motion assessment, hands-on check-in, massage applied directly to the neck, addressing compensatory patterns, and integration (reestablishment within a patient of being in a unified body after having received intensive isolated work). Therapists (8 licensed therapists with at least 5 years of experience) were given time limits for each part of the massage and permitted to use a broad range of massage techniques. No self-care recommendations were permitted. Duration 4 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA (n=37) Intervention 4: Manual therapy - Soft tissue technique. 3 x 30 min/week massage - included range of motion assessment, hands-on check-in, massage applied directly to the neck, addressing compensatory patterns, and integration (reestablishment within a patient of being in a unified body after having received intensive isolated work). Therapists (8 licensed therapists with at least 5 years of experience) were given time limits for each part of the massage and permitted to use a broad range of massage techniques. No self-care recommendations were permitted. Duration 4 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA (n=39) Intervention 5: Manual therapy - Soft tissue technique. 3 x 60 min/week massage - included range of motion assessment, hands-on check-in, massage applied directly to the neck, addressing compensatory patterns, and integration (reestablishment within a patient of being in a unified body after having received

	intensive isolated work). Therapists (8 licensed therapists with at least 5 years of experience) were given time limits for each part of the massage and permitted to use a broad range of massage techniques. No self-care recommendations were permitted. Duration 4 weeks . Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA (n=37) Intervention 6: Usual care. Waiting list. Duration 4 weeks. Concurrent medication/care: not reported Indirectness: No indirectness; Indirectness comment: NA
Funding	Academic or government funding (National Center for Complementary and Alternative Medicine, National Institutes of Health.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus USUAL CARE

Protocol outcome 1: Pain reduction
- Actual outcome: Numeric rating scale (1x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -1.21 (SD 1.98); n=38, Group 2: mean -0.51 (SD 2.52); n=35; NRS 0-10 Top=High is poor outcome; Comments: Baseline values: 1x60min/week 5.9 (1.5), control 5.6 (1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 2: Physical function
- Actual outcome: Neck Disability Index (1x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -0.86 (SD 3.85); n=38, Group 2: mean 1.45 (SD 4.98); n=35; NDI 0-50 Top=High is poor outcome; Comments: Baseline values: 1x60min/week 14 (4.6), control 13.4 (4.8)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 3: Psychological distress
- Actual outcome: Perceived Stress Scale (1x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -1.1 (SD 3.77); n=38, Group 2: mean -0.42 (SD 6.21); n=37; perceived stress scale 0-40 Top=High is poor outcome; Comments: adjusted for baseline Neck Disability Index, neck pain intensity, age, sex, duration of neck pain more than 5 years, use of medications for neck pain, race (white non-Hispanic vs. other) and baseline score for this scale SDs calculated from CIs
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus USUAL CARE

Protocol outcome 1: Pain reduction
- Actual outcome: Numeric rating scale (2x30min/week) at 5 weeks (1 week post intervention); Group 1: mean -1.66 (SD 1.98); n=38, Group 2: mean -0.51 (SD 2.52); n=35; NRS 0-10 Top=High is poor outcome; Comments: Baseline values: 2x30min/week 5.8 (1.4), control 5.6 (1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 1, Reason: 1 lost to follow up; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 2: Physical function
- Actual outcome: Neck Disability Index (2x30min/week) at 5 weeks (1 week post intervention); Group 1: mean -0.89 (SD 4.51); n=38, Group 2: mean 1.45 (SD 4.98); n=35; NDI 0-50 Top=High is poor outcome; Comments: Baseline values: 2x30min/week 13.4 (3.8), control 13.4 (4.8)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 1, Reason: 1 lost to follow up; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 3: Psychological distress
- Actual outcome: Perceived Stress Scale (2x30min/week) at 5 weeks (1 week post intervention); Group 1: mean -1.6 (SD 5.5); n=38, Group 2: mean -0.42 (SD 6.21); n=37; perceived stress scale 0-40 Top=High is poor outcome; Comments: adjusted for baseline Neck Disability Index, neck pain intensity, age, sex, duration of neck pain more than 5 years, use of medications for neck pain, race (white non-Hispanic vs. other) and baseline score for this scale SDs calculated from CIs
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus USUAL CARE

Protocol outcome 1: Pain reduction
- Actual outcome: Numeric rating scale (3x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -2.74 (SD 1.53); n=38, Group 2: mean -0.51 (SD 2.52); n=35; NRS 0-10 Top=High is poor outcome; Comments: Baseline values: 3x60min/week 5.7 (1.2), control 5.6 (1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 3, Reason: 2 withdrew, 1 lost to follow up ; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 2: Physical function
- Actual outcome: Neck Disability Index (2x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -2.06 (SD 4.55); n=38, Group 2: mean 1.45 (SD 4.98); n=35; NDI 0-50 Top=High is poor outcome; Comments: Baseline values: 2x60min/week 13.7 (5.1), control 13.4 (4.8)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 3, Reason: 2 withdrew, 1 lost to follow up; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 3: Psychological distress
- Actual outcome: Perceived Stress Scale (2x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -1.5 (SD 4.88); n=38, Group 2: mean -0.42 (SD 6.21); n=37; perceived stress scale 0-40 Top=High is poor outcome; Comments: adjusted for baseline Neck Disability Index, neck pain intensity, age, sex, duration of neck pain more than 5 years, use of medications for neck pain, race (white non-Hispanic vs. other) and baseline score for this scale SDs calculated from CIs
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 1, Reason: 1 lost to follow up; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus USUAL CARE

Protocol outcome 1: Pain reduction
- Actual outcome: Numeric rating scale (3x30min/week) at 5 weeks (1 week post intervention); Group 1: mean -1.62 (SD 1.7); n=34, Group 2: mean -0.51 (SD 2.52); n=35; NRS 0-10 Top=High is poor outcome; Comments: Baseline values: 3x30min/week 6.1 (1.5), control 5.6 (1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 1, Reason: 1 lost to follow up; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 2: Physical function
- Actual outcome: Neck Disability Index (3x30min/week) at 5 weeks (1 week post intervention); Group 1: mean 0.05 (SD 3.88); n=34, Group 2: mean 1.45 (SD 4.98); n=35; NDI 0-50 Top=High is poor outcome; Comments: Baseline values: 3x30min/week 13.1 (5.6), control 13.4 (4.8)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 1, Reason: 1 lost to follow up ; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 3: Psychological distress

- Actual outcome: Perceived Stress Scale (3x30min/week) at 5 weeks (1 week post intervention); Group 1: mean -3.7 (SD 5.59); n=37, Group 2: mean -0.42 (SD 6.21); n=37; perceived stress scale 0-40 Top=High is poor outcome; Comments: adjusted for baseline Neck Disability Index, neck pain intensity, age, sex, duration of neck pain more than 5 years, use of medications for neck pain, race (white non-Hispanic vs. other) and baseline score for this scale SDs calculated from CIs
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 3, Reason: 2 withdrew, 1 lost to follow up ; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus USUAL CARE

Protocol outcome 1: Pain reduction
- Actual outcome: Numeric rating scale (2x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -2.21 (SD 1.88); n=38, Group 2: mean -0.51 (SD 2.52); n=35; NRS 0-10 Top=High is poor outcome; Comments: Baseline values: 2x60min/week 5.6 (1.1), control 5.6 (1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 2: Physical function
- Actual outcome: Neck Disability Index (3x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -4.36 (SD 5.94); n=38, Group 2: mean 1.45 (SD 4.98); n=35; NDI 0-50 Top=High is poor outcome; Comments: Baseline values: 3x60min/week 14.3 (5.5), control 13.4 (4.8)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain ; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcome 3: Psychological distress
- Actual outcome: Perceived Stress Scale (3x60min/week) at 5 weeks (1 week post intervention); Group 1: mean -1.5 (SD 5.58); n=39, Group 2: mean -0.42 (SD 6.21); n=37; perceived stress scale 0-40 Top=High is poor outcome; Comments: adjusted for baseline Neck Disability Index, neck pain intensity, age, sex, duration of neck pain more than 5 years, use of medications for neck pain, race (white non-Hispanic vs. other) and baseline score for this scale SDs calculated from CIs

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics were well balanced across groups, except for the percent of participants of white, non-Hispanic race/ethnicity and the percent having more than 7 days of usual activity restricted because of neck pain; Group 1 Number missing: 1, Reason: 1 lost to follow up; Group 2 Number missing: 2, Reason: 1 withdrew, 1 lost to follow up

Protocol outcomes not reported by the study	Health related quality of life ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Sobhani 2017[256]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=39)
Countries and setting	Conducted in Iran; Setting: Not stated.
Line of therapy	Unclear
Duration of study	Intervention time: 10 days
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients with cervical spine pain originating from muscles referred for physical therapy management were assessed for inclusion criteria. Cervical pain was explained as mechanical pain in cervical region muscles that can be aggravated with sustained posture and different cervical motions.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria included: 1) bilateral involving upper trapezius and levator scapulae muscles, 2) Pain for at least 3 months, 3) a pain intensity of 2 out of 10 based on visual analogue scale (VAS), 4) symptoms of neck pain provoked either by neck postures or neck motions, 5) neck disability index over or equal to 15 points, 6) cervical spine range of motion restriction, and 7) MTrPs in upper trapezius and levator scapulae muscles.
Exclusion criteria	Exclusion criteria were identified as: 1) Manipulation application contraindication, 2) Orofacial pain or temporomandibular joint disorders, 3) History of traumatic injuries (such as contusions and fractures), 4) systemic diseases (fibromyalgia and psoriatic arthritis), 5) neurological diseases, 6) presence of neck pain concomitant to headache (i e, tension type headache or migraine), 7) history of surgery in cervical region, 8) clinical diagnosis of cervical radiculopathy or myelopathy, 9) unilateral neck pain, 10) needle phobia, 11) history of skin irritability, and 12) previous history of receiving physical therapy, KT or manipulation in the past 6 months.
Age, gender and ethnicity	Age - Mean (SD): manual therapy group 35.9 (11.4); dry needling group 34.6 (10.5). Gender (M:F): 57 males only. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: No 8. Homeless: No 9. Learning difficulties: No 10. Sensory impairment: No
Extra comments	Duration of symptoms in months (SD): manual therapy group 15.1 (7.5) ; dry needling group 12.6 (4.4)
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Manual therapy - Mixed modality manual therapy. The subjects in the second group received a bilateral manual therapy treatment based on the ischemic compression (IC) technique over both

	the levator scapulae and upper trapezius muscles, but also a dynamic soft tissue mobilisation (DSTM) was applied on the upper trapezius for 4 minutes. Thereafter, 3 manual therapy techniques were performed by the physical therapist as follows: 1) Anterior-posterior mobilisation of the upper cervical spine for 4 minutes, 2) Cervical lateral glide mobilisation technique, and 3) Neural thoracic mobilisation. Duration 10 days (5 sessions). Concurrent medication/care: Not stated. Indirectness: No indirectness (n=13) Intervention 2: Acupuncture/dry needling. Bilateral dry needling method for upper trapezius and levator scapulae muscles followed by passive stretching were the treatment options for the subjects in the first group. Based on the high prevalence of myofascial trigger points in upper trapezius and levator scapulae muscles in patients with cervical spine pain, these 2 muscles were selected for dry needling application. After 20 minutes of needling, passive stretching was bilaterally applied to the levator scapulae and trapezius muscles. Duration 10 days (5 sessions). Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MODALITY MANUAL THERAPY versus ACUPUNCTURE/DRY NEEDLING

Protocol outcome 1: Pain reduction
- Actual outcome: Pain intensity on Visual Analogue Scale (VAS) at Post-treatment (10 days); Group 1: mean 33.8 (SD 12.6); n=13, Group 2: mean 39.2 (SD 20.1); n=13; Visual Analogue Scale (mm) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Manual therapy group 53.8 (16) Dry needling group 56.1 (19.3)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Physical function
- Actual outcome: Neck Disability Index (NDI) at Post-treatment (10 days); Group 1: mean 19.6 (SD 6.5); n=13, Group 2: mean 16.7 (SD 3.9); n=13; Neck Disability Index (NDI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Manual therapy group 24.4 (7.6) Dry needling group 21.6 (4.8)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 3: Psychological distress
- Actual outcome: Pain Catastrophizing Scale (PCS) at Post-treatment (10 days); Group 1: mean 17 (SD 6.7); n=13, Group 2: mean 15.2 (SD 4.9); n=13; Pain Catastrophizing Scale (PCS) 0-52 Top=High is poor outcome; Comments: Baselines, mean (SD): Manual therapy group 23.7 (10.7) Dry needling group 19.8 (5.5)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcomes not reported by the study	Health related quality of life ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Zaproudina 2007[290]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=105)
Countries and setting	Conducted in Finland; Setting: Not stated.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5-10 weeks + 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Minimum 3 out of 10 on VAS pain scale. Other assessment not stated.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with chronic nonspecific neck pain - clinical diagnosis of "tension neck" without radicular arm symptoms, minimum 3 out of 10 on VAS pain scale, between 28 and 50 years of age.
Exclusion criteria	Previous neck surgery, current nerve root entrapment, spinal cord compression, severe neurologic, metabolic, psychiatric or cardiovascular diseases, or any therapy or sick leave during the previous month.
Recruitment/selection of patients	Advert in the local newspaper was used for recruiting voluntary subjects.
Age, gender and ethnicity	Age - Mean (SD): Mobilisation group 41.2 (5.7); Massage group 42.4 (5.9). Gender (M:F): 37 men / 68 women. Ethnicity: Not stated.
Further population details	1. Chronic orofascial pain: No 2. Chronic primary musculoskeletal pain: Yes 3. Chronic visceral pain: No 4. Chronic widespread pain: No 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: No 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment: Not stated / Unclear
Extra comments	Chronic nonspecific neck pain. Neck pain duration in years (SD): mobilisation group 11.7 (6.2); massage group 11.2 (7.3).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Manual therapy - Soft tissue technique. Massage intervention: upper body massage was done by registered therapists, five 1-hour sessions per subject. Timetables were adjusted to each patient. Duration 5 sessions over 5-10 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=35) Intervention 2: Manual therapy - Manipulation/mobilisation. Mobilisation: Traditional bone setting was carried out by experienced Finnish bone setters/ On average, five 1.5 hour sessions per patient were provided with 1- or 2-week intervals. Duration 5 sessions over 5-10 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness

Funding	Other (This study was supported by Finland's Slot Machine Association RAY and performed in collaboration with the Folk Healing Association, Finland.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOFT TISSUE TECHNIQUE versus MANIPULATION/MOBILISATION Protocol outcome 1: Pain reduction - Actual outcome: Self-reported pain on VAS at 1 month follow-up; Group 1: mean 25.4 (SD 22); n=33, Group 2: mean 17.9 (SD 18); n=35; Visual analogue scale (VAS) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Soft tissue massage group 46.6 (22) Mobilisation group 49.5 (21) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Complete patient characteristics not published, but outcomes comparable at baseline.; Group 1 Number missing: 2, Reason: Reasons for dropout not stated; Group 2 Number missing: 0 Protocol outcome 2: Physical function - Actual outcome: Perceived disability on Neck Disability Index (NDI) at 1 month follow-up; Group 1: mean 15.3 (SD 10); n=33, Group 2: mean 11.7 (SD 9); n=35; Neck Disability Index (NDI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): Soft tissue massage group 26.0 (11) Mobilisation group 24.1 (8) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Complete patient characteristics not published, but outcomes comparable at baseline.; Group 1 Number missing: 2, Reason: Reasons for dropout not stated; Group 2 Number missing: 0 Protocol outcome 3: Discontinuation - Actual outcome: Drop out at 1 month follow-up; Group 1: 2/35, Group 2: 0/35; Comments: Reasons for dropout not stated. Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Complete patient characteristics not published, but outcomes comparable at baseline.; Group 1 Number missing: 2, Reason: Reasons for dropout not stated; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health related quality of life ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Appendix E: Forest plots

E.1 Mixed modality manual therapy vs. Usual care

Figure 2: Pain reduction at ≤3 months (Brief Pain Inventory; VAS 0-10, final values and change scores)

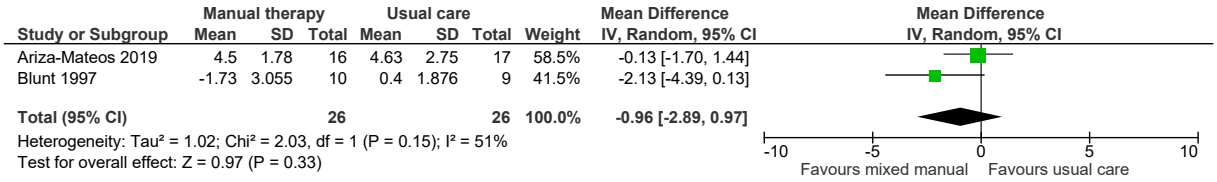


Figure 3: Pain reduction at >3 months (Brief Pain Inventory, 0-10, final scores, high is poor outcome)

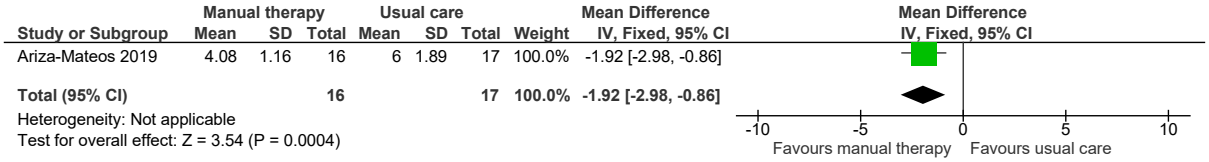


Figure 4: Physical function at ≤3 months (Oswestry Disability Index, 0-100, change scores and final scores, high is poor outcome)

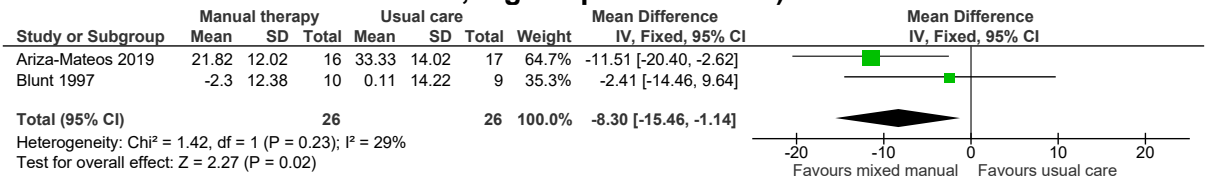


Figure 5: Physical function at >3 months (Oswestry Disability Index, 0-100, final scores, high is poor outcome)

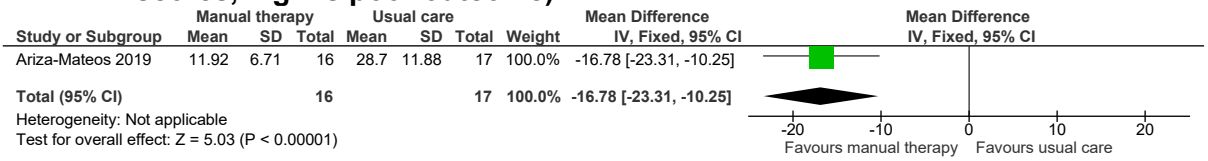


Figure 6: Pain interference at ≤3 months (Brief pain inventory – interference, 0-10, final values, high is poor outcome)

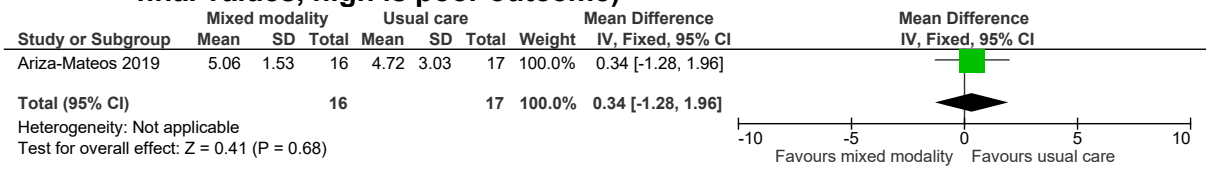


Figure 7: Pain interference at >3 months (Brief pain inventory – interference, 0-10, final values, high is poor outcome)

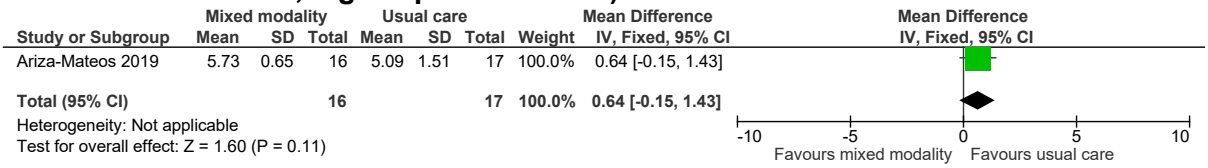
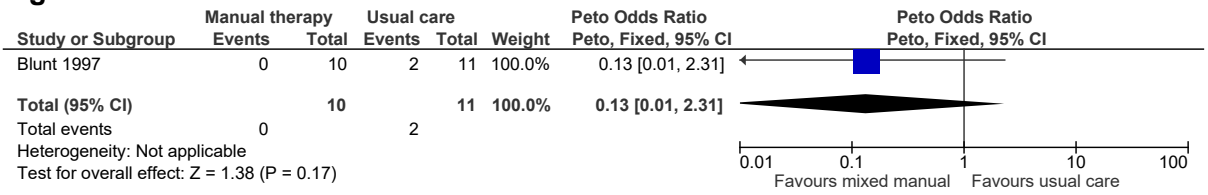


Figure 8: Discontinuation at ≤3 months



E.2 Soft tissue technique vs. usual care

Figure 9: Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values and change scores)

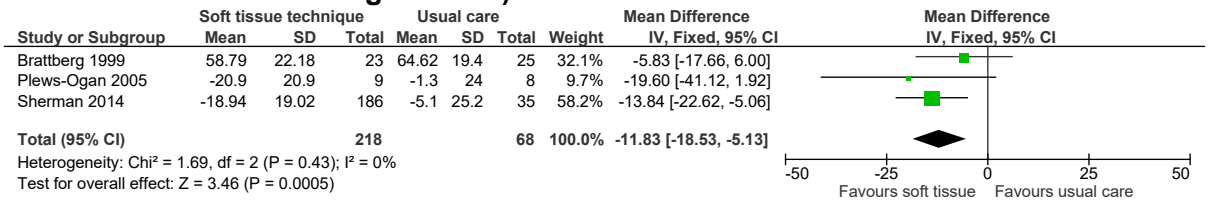


Figure 10: Health related quality of life at ≤3 months (Fibromyalgia Impact Questionnaire, 0-100, high is poor outcome, final score)

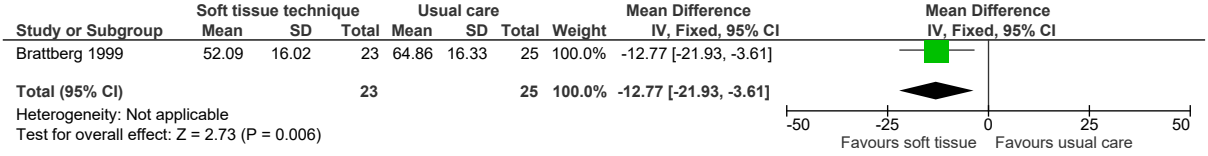


Figure 11: Health related quality of life at ≤3 months (SF-12 Mental health, 0-100, high is good outcome, change score)

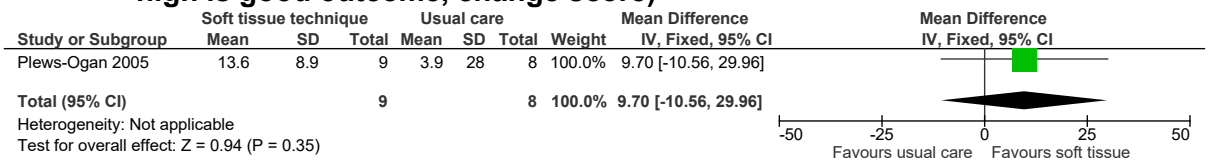


Figure 12: Health related quality of life at >3 months (Fibromyalgia Impact Questionnaire, 0-100, high is poor outcome, final score)

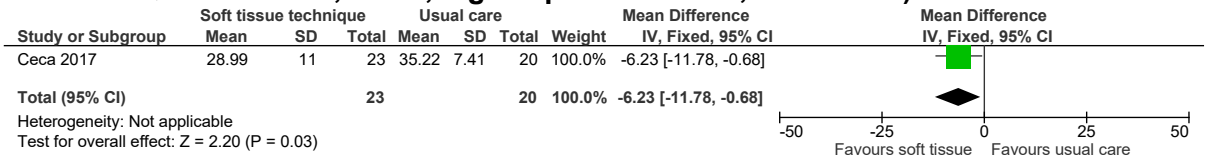


Figure 13: Physical function at ≤3 months (Disability Rating Index, 0-100, high is poor outcome, final score)

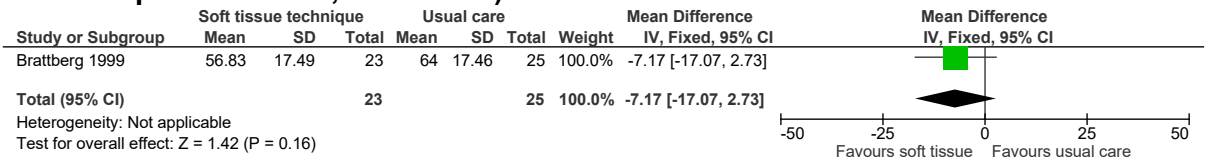


Figure 14: Physical function at ≤3 months (Neck Disability Index, 0-50, high is poor outcome, change scores)

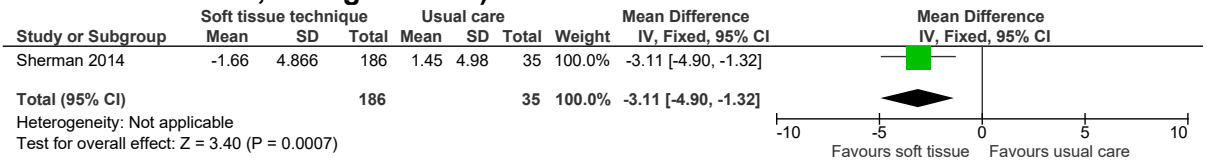


Figure 15: Psychological distress at ≤3 months (Hospital Anxiety and Depression Scale depression subscale, 0-21, high is poor outcome, final score)

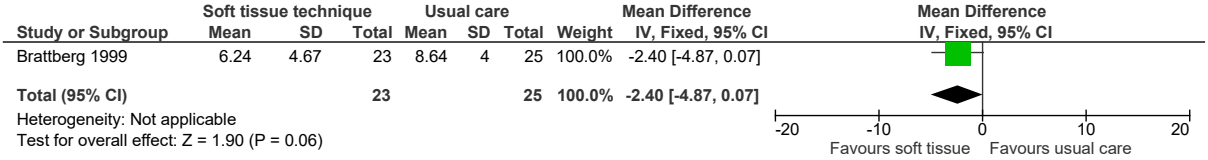


Figure 16: Psychological distress at ≤3 months (Hospital Anxiety and Depression Scale anxiety subscale, 0-21, high is poor outcome, final score)

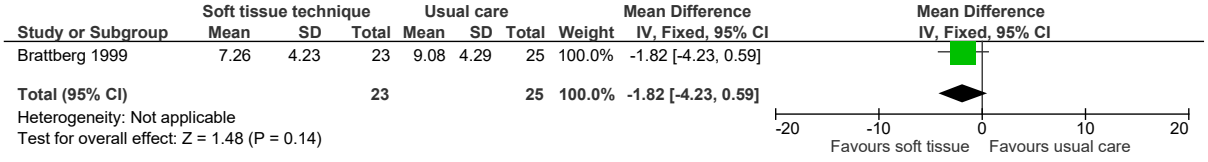


Figure 17: Psychological distress at ≤3 months (Perceived Stress Scale, 0-40, high is poor outcome, change scores)

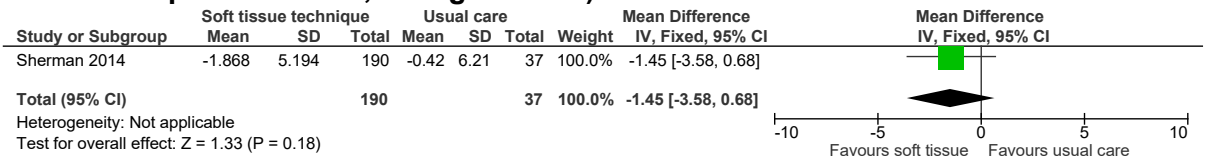


Figure 18: Sleep disturbance at ≤3 months (mean value for 10 questions about sleep, 0-5, high is poor outcome, final score)

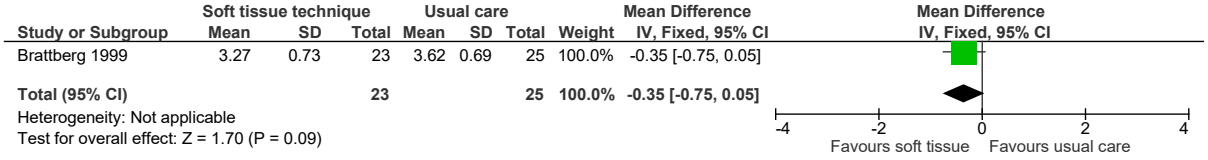


Figure 19: Discontinuation at ≤3 months

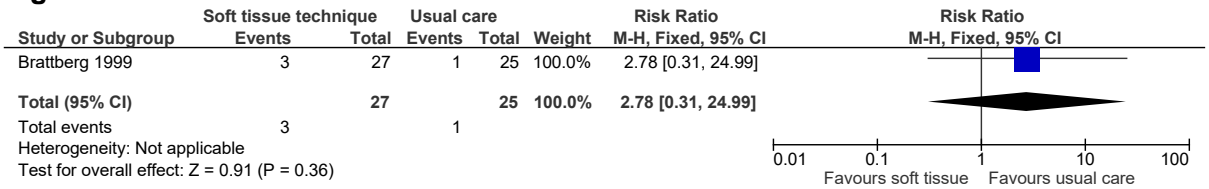
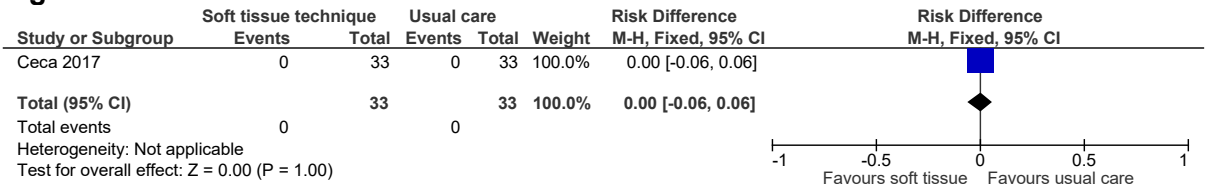


Figure 20: Discontinuation at >3 months



E.3 Manipulation/mobilisation vs. usual care

Figure 21: Pain reduction at ≤3 months (visual analogue scale 0-10; high is poor outcome; final values)

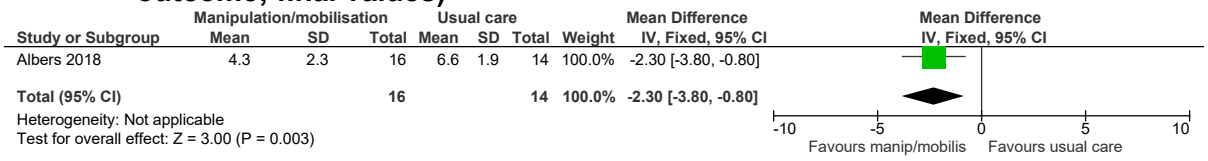


Figure 22: Quality of life at ≤3 months (Fibromyalgia Impact Questionnaire 0-100; high is poor outcome; final values)

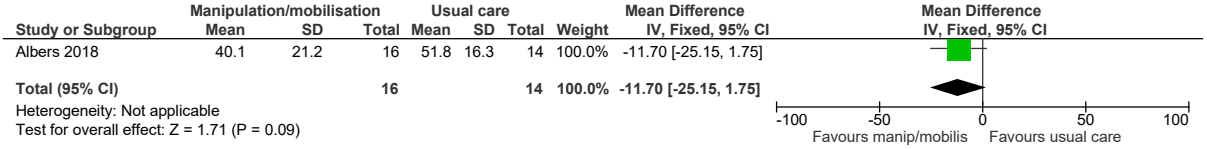
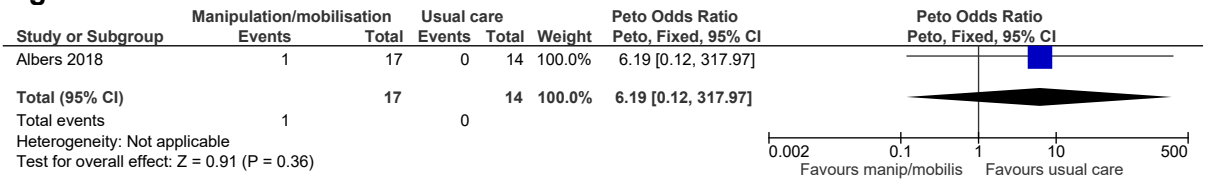


Figure 23: Discontinuation at ≤3 months



E.4 Mixed modality manual therapy vs. soft tissue techniques

Figure 24: Pain reduction at ≤3 months (Numeric Pain Rating Scale, 0-10, high is poor outcome, final score)

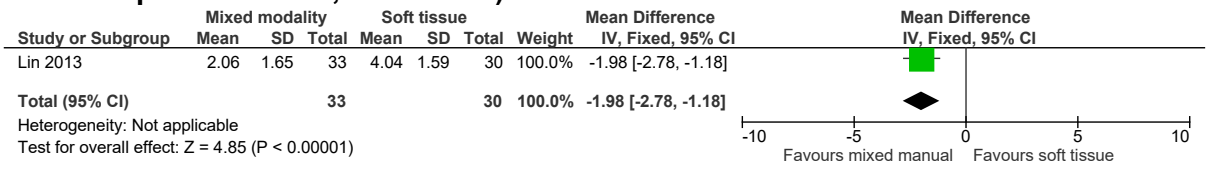


Figure 25: Pain reduction at >3 months (Numeric Pain Rating Scale, 0-10, high is poor outcome, final score)

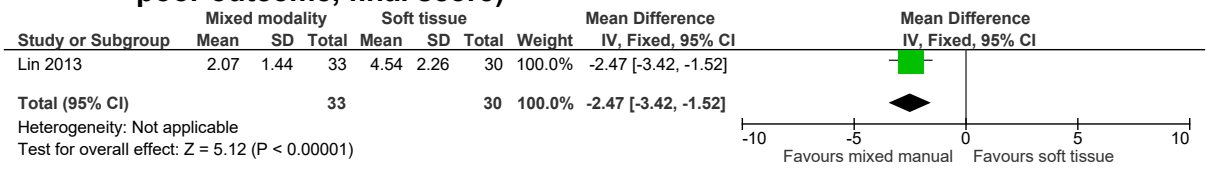
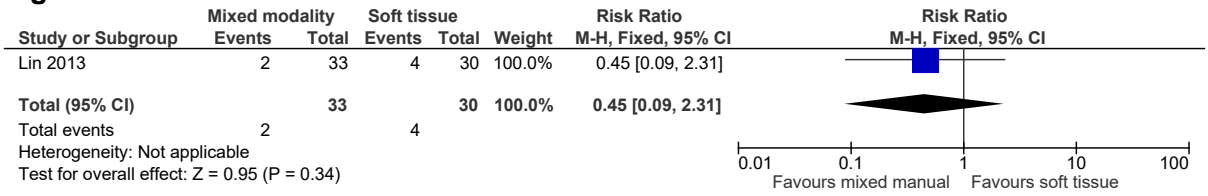
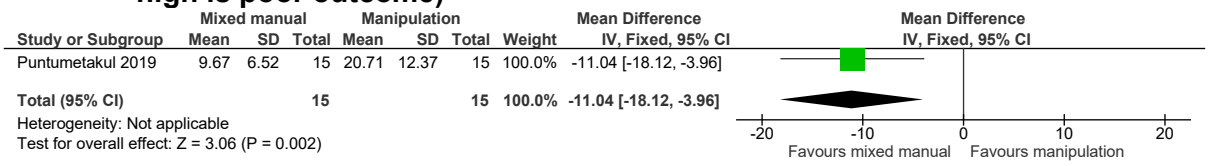


Figure 26: Discontinuation at ≤3 months



E.5 Mixed modality manual therapy vs. manipulation/mobilisation

Figure 27: Pain reduction at ≤3 months (pain at rest on VAS, 0-100, final scores, high is poor outcome)

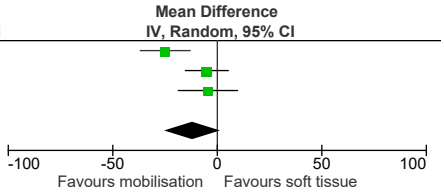


E.6 Manipulation/mobilisation vs. soft tissue techniques

Figure 28: Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values)

Study or Subgroup	Mobilisation Mean	SD	Total	Soft tissue massage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Campa-Moran 2015	9.4	14.79	12	34.3	14.79	12	33.7%	-24.90 [-36.73, -13.07]
Fitzgerald 2012	38	23	38	43	23	40	36.1%	-5.00 [-15.21, 5.21]
Madson 2010	16.45	13.69	11	20.91	20.46	12	30.2%	-4.46 [-18.58, 9.66]
Total (95% CI)			**61**			**64**	**100.0%**	**-11.53 [-24.86, 1.80]**

Heterogeneity: Tau² = 100.97; Chi² = 7.44, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 1.70 (P = 0.09)



NB. Heterogeneity was not explained by subgroup analysis.

Figure 29: Pain reduction at >3 months (pain reduction on VAS, 0-100, high is poor outcome, final score)

Study or Subgroup	Mobilisation Mean	SD	Total	Soft tissue massage Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zaproudina 2007	17.9	18	35	25.4	22	33	100.0%	-7.50 [-17.09, 2.09]
Total (95% CI)			**35**			**33**	**100.0%**	**-7.50 [-17.09, 2.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)

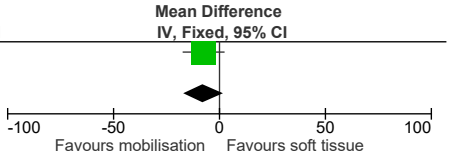


Figure 30: Health related quality of life at ≤3 months (SF-12 Physical component, 0-100, high is good outcome, final values)

Study or Subgroup	Mobilisation Mean	SD	Total	Soft tissue massage Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fitzgerald 2012	45.6	9.4	38	46	10.5	40	100.0%	-0.40 [-4.82, 4.02]
Total (95% CI)			**38**			**40**	**100.0%**	**-0.40 [-4.82, 4.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

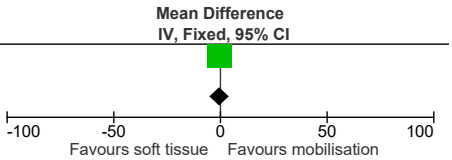


Figure 31: Health related quality of life at ≤3 months (SF-12 Mental component, 0-100, high is good outcome, final values)

Study or Subgroup	Mobilisation Mean	SD	Total	Soft tissue massage Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fitzgerald 2012	45	10.8	38	49.3	8.5	40	100.0%	-4.30 [-8.63, 0.03]
Total (95% CI)			**38**			**40**	**100.0%**	**-4.30 [-8.63, 0.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.95 (P = 0.05)

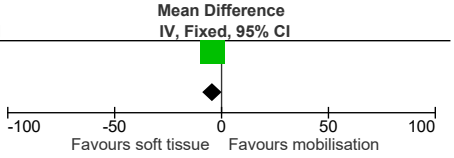


Figure 32: Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values)

Study or Subgroup	Mobilisation Mean	SD	Total	Soft tissue massage Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Campa-Moran 2015	10	5.51	12	15.2	5.51	12	72.9%	-5.20 [-9.61, -0.79]
Madson 2010	11.28	7.22	12	16.16	10.56	12	27.1%	-4.88 [-12.12, 2.36]
Total (95% CI)			**24**			**24**	**100.0%**	**-5.11 [-8.88, -1.35]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.66 (P = 0.008)

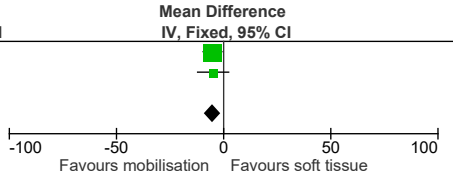


Figure 33: Physical function at >3 months (Neck Disability Index, 0-100, high is poor outcome, final values)

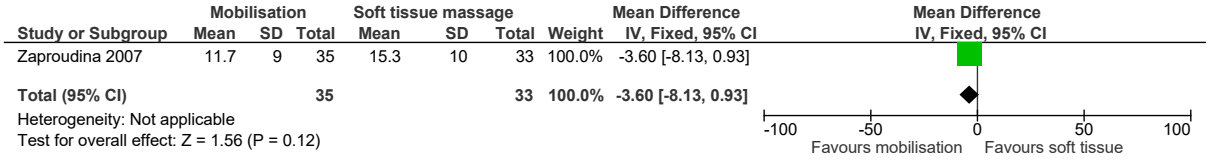


Figure 34: Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values)

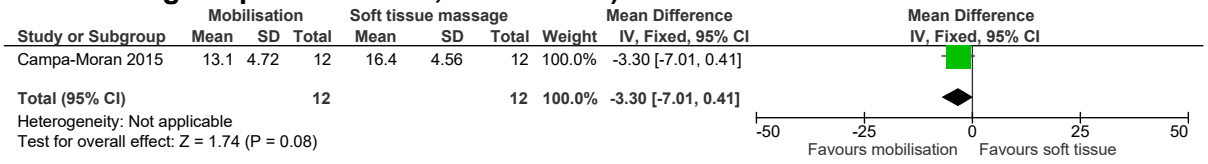


Figure 35: Discontinuation at ≤3 months

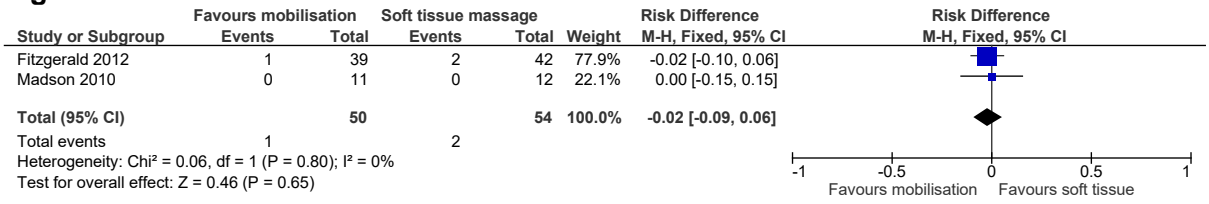
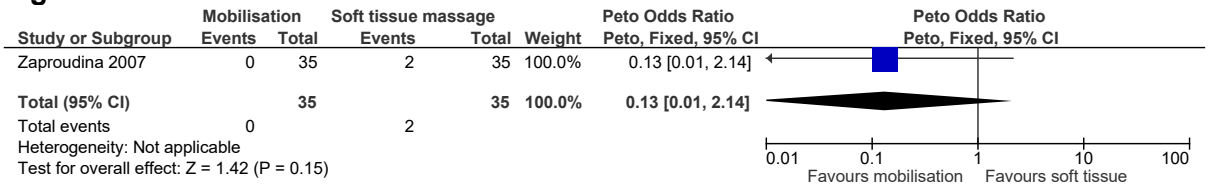


Figure 36: Discontinuation at >3 months



E.7 Mixed modality manual therapy vs. acupuncture/dry needling

Figure 37: Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final score)

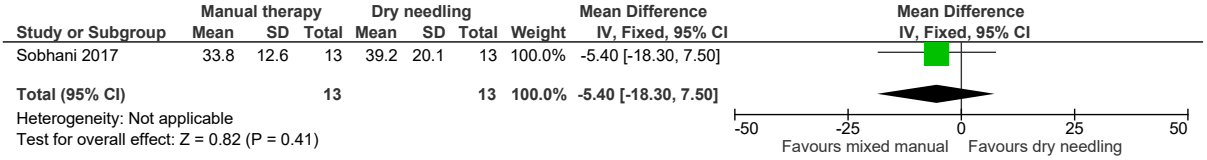


Figure 38: Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final score)

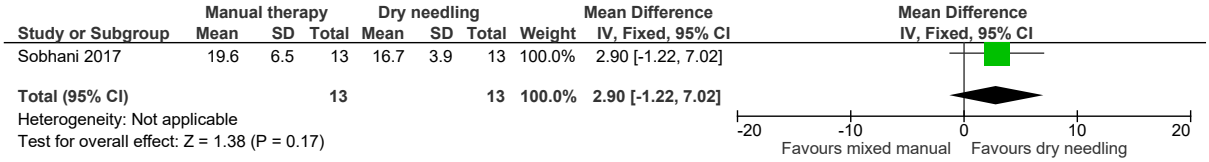
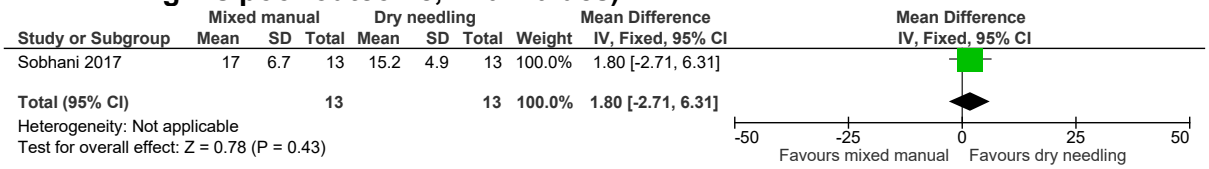


Figure 39: Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values)



E.8 Soft tissue techniques vs. acupuncture/dry needling

Figure 40: Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values)

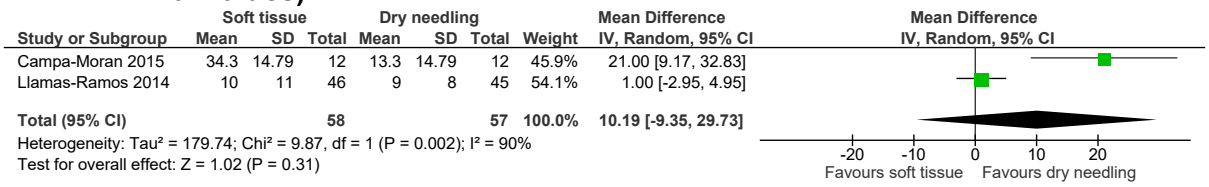


Figure 41: Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values)

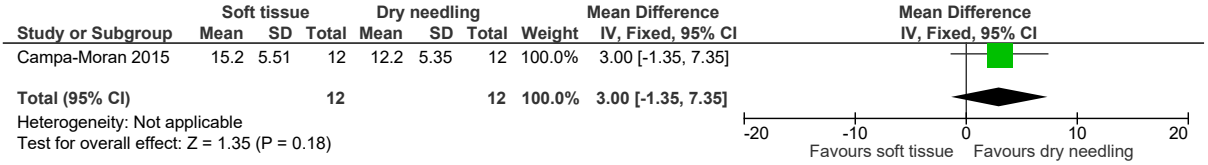


Figure 42: Psychological distress at ≤3 months (Pain Catastrophising Scale, 0-52, high is poor outcome, final values)

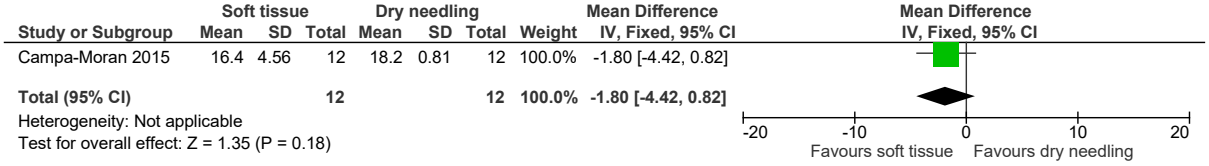
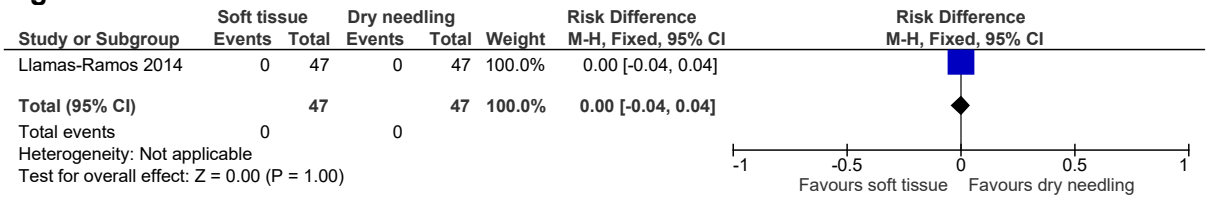


Figure 43: Discontinuation at ≤3 months



E.9 Manipulation/mobilisation vs. acupuncture/dry needling

Figure 44: Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values)

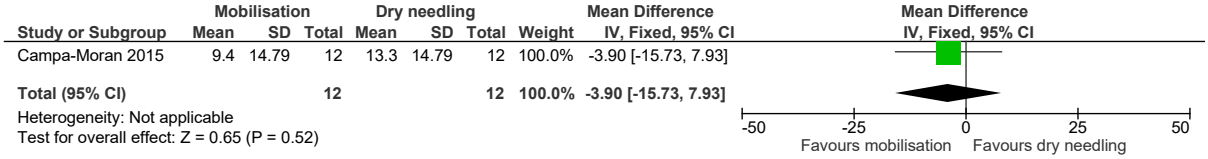


Figure 45: Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values)

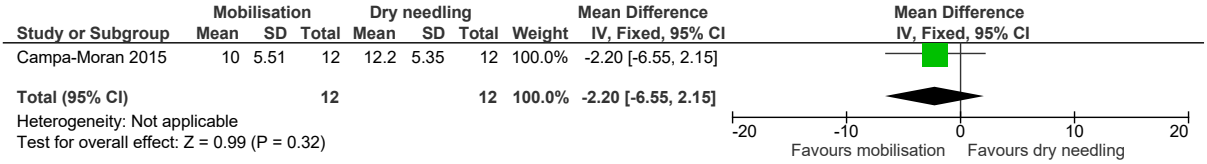
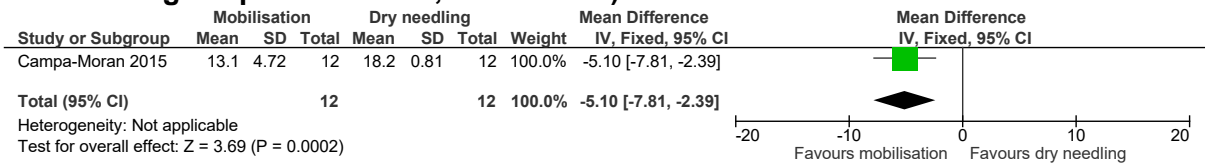


Figure 46: Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values)



Appendix F: GRADE tables

Table 15: Clinical evidence profile: mixed modality manual therapy vs. usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed modality manual therapy	Usual care	Relative (95% CI)	Absolute		
Pain reduction at ≤3 months (Brief Pain Inventory; VAS 0-10, final values and change scores, high scores are poor outcome) (follow-up 4 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	26	-	MD 0.96 lower (2.89 lower to 0.97 higher)	⊕⊕OO LOW	CRITICAL
Pain reduction at >3 months (Brief Pain Inventory, 0-10, final scores, high scores are poor outcome) (follow-up 18 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	17	-	MD 1.92 lower (2.98 to 0.86 lower)	⊕⊕OO LOW	CRITICAL
Physical function at ≤3 months (Oswestry Disability Index, 0-100, change scores and final scores, high is poor outcome) (follow-up 6 weeks; range of scores: 0-100; Better indicated by lower values)												
2	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	26	26	-	MD 8.3 lower (15.46 to 1.14 lower)	⊕OOO VERY LOW	CRITICAL
Physical function at >3 months (Oswestry Disability Index, 0-100, final scores, high is poor outcome) (follow-up 18 weeks; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	17	-	MD 16.78 lower (23.31 to 10.25 lower)	⊕⊕OO LOW	CRITICAL
Pain interference at >3 months (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	17	-	MD 0.13 lower (1.7 lower to 1.44 higher)	⊕OOO VERY LOW	CRITICAL

Pain interference at ≤3 months (follow-up 18 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	17	-	MD 0.64 higher (0.15 lower to 1.43 higher)	⊕OOO VERY LOW	CRITICAL
Discontinuation at ≤3 months (follow-up 4 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/10 (0%)	18.2%	RR 0.22 (0.01 to 4.06)	142 fewer per 1000 (from 180 fewer to 557 more)	⊕OOO VERY LOW	IMPORTANT

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

Table 16: Clinical evidence profile: soft tissue technique vs. usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Soft tissue technique**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final score) (follow-up 5-10 weeks; range of scores: 0-100; Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	218	68	-	MD 11.83 lower (18.53 to 5.13 lower)	⊕⊕OO LOW	CRITICAL
Health related quality of life at ≤3 months (Fibromyalgia Impact Questionnaire, 0-100, high is poor outcome, final score) (follow-up 10 weeks; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	23	25	-	MD 12.77 lower (21.93 to 3.61 lower)	⊕OOO VERY LOW	CRITICAL
Health related quality of life at ≤3 months (SF-12 Mental health, 0-100, high is good outcome, change score) (follow-up 8 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9	8	-	MD 9.7 higher (10.56 lower to 29.96 higher)	⊕OOO VERY LOW	CRITICAL

Health related quality of life at >3 months (Fibromyalgia Impact Questionnaire, 0-100, high is poor outcome, final score) (follow-up 20 weeks; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23	20	-	MD 6.23 lower (11.78 to 0.68 lower)	⊕OOO VERY LOW	CRITICAL
Physical function at ≤3 months (Disability Rating Index, 0-100, high is poor outcome, final score) (follow-up 10 weeks; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	23	25	-	MD 7.17 lower (17.07 lower to 2.73 higher)	⊕OOO VERY LOW	CRITICAL
Physical function at ≤3 months (Neck Disability Index, 0-50, high is poor outcome, change scores) (follow-up 5 weeks; range of scores: 0-50; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	186	35	-	MD 3.11 lower (4.9 to 1.32 lower)	⊕⊕OO LOW	CRITICAL
Psychological distress at ≤3 months (Hospital Anxiety and Depression Scale depression subscale, 0-21, high is poor outcome, final score) (follow-up 10 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	23	25	-	MD 2.4 lower (4.87 lower to 0.07 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at ≤3 months (Hospital Anxiety and Depression Scale anxiety subscale, 0-21, high is poor outcome, final score) (follow-up 10 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	23	25	-	MD 1.82 lower (4.23 lower to 0.59 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at ≤3 months (Perceived Stress Scale, 0-40, high is poor outcome, change scores) (follow-up 5 weeks; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	190	37	-	MD 1.45 lower (3.58 lower to 0.69 higher)	⊕⊕OO LOW	CRITICAL
Sleep disturbance at ≤3 months (mean value for 10 questions about sleep, 0-5, high is poor outcome, final score) (follow-up 10 weeks; range of scores: 0-5; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	23	25	-	MD 0.35 lower (0.75 lower to 0.05 higher)	⊕OOO VERY LOW	IMPORTANT

Discontinuation at ≤3 months (follow-up 10 weeks)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/27 (11.1%)	2/25 (8%)	RR 2.78 (0.31 to 24.99)	142 more per 1000 (from 55 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Discontinuation at >3 months (follow-up 20 weeks)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/33 (0%)	0%	RD 0 (-0.06 to 0.06)	0 more per 1000 (from 60 fewer to 60 more)	⊕OOO VERY LOW	IMPORTANT

1 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
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Indirectness in comparator for Brattberg 1999: half of the usual care control group received different care (group discussions once per week).

Table 17: Clinical evidence profile: manipulation/mobilisation vs. usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Manipulation/mobilisation**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Pain reduction at ≤3 months (final values) (follow-up 12 weeks; measured with: VAS 0-10; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	14	-	MD 2.3 lower (3.8 to 0.8 lower)	⊕⊕OO LOW	CRITICAL
Quality of life at ≤3 months (final values) (follow-up 12 weeks; measured with: Fibromyalgia Impact Questionnaire ; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	14	-	MD 11.7 lower (25.15 lower to 1.75 higher)	⊕⊕OO LOW	CRITICAL
Discontinuation (follow-up 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/17 (5.9%)	0%	Peto OR 6.19 (0.12 to 317.97)	58 more per 1000 (from 97 less to 215 more)	⊕OOO VERY LOW	IMPORTANT

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

Table 18: Clinical evidence profile: mixed modality manual therapy vs. soft tissue technique

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed modality manual therapy**	**Soft tissue technique**	**Relative (95% CI)**	**Absolute**		
Pain reduction at ≤3 months (Numeric Pain Rating Scale, 0-10, high is poor outcome, final score) (follow-up 24 days; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	30	-	MD 1.98 lower (2.78 to 1.18 lower)	⊕⊕⊕O MODERATE	CRITICAL
Pain reduction at >3 months (Numeric Pain Rating Scale, 0-10, high is poor outcome, final score) (follow-up 4 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	30	-	MD 2.47 lower (3.42 to 1.52 lower)	⊕⊕OO LOW	CRITICAL
Discontinuation at ≤3 months (follow-up 24 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/33 (6.1%)	13.3%	RR 0.45 (0.09 to 2.31)	73 fewer per 1000 (from 121 fewer to 174 more)	⊕OOO VERY LOW	IMPORTANT

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

Table 19: Clinical evidence profile: manipulation/mobilisation vs. soft tissue technique

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manipulation/mobilisation	Soft tissue technique	Relative (95% CI)	Absolute		
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values and change scores) (follow-up 9-84 days; range of scores: 0-100; Better indicated by lower values)												
3	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	61	64	-	MD 11.53 lower (24.86 lower to 1.8 higher)	⊕OOO VERY LOW	CRITICAL
Pain reduction at >3 months (pain reduction on VAS, 0-100, high is poor outcome, final score) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	35	33	-	MD 7.5 lower (17.09 lower to 2.09 higher)	⊕⊕OO LOW	CRITICAL
Health related quality of life at ≤3 months (SF-12 Physical component, 0-100, high is good outcome, final values and change scores) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	40	-	MD 0.4 lower (4.82 lower to 4.02 higher)	⊕⊕OO LOW	CRITICAL
Health related quality of life at ≤3 months (SF-12 Mental component, 0-100, high is good outcome, final values and change scores) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	38	40	-	MD 4.3 lower (8.63 lower to 0.03 higher)	⊕OOO VERY LOW	CRITICAL
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values) (follow-up 9-28 days; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	24	24	-	MD 5.11 lower (8.88 to 1.35 lower)	⊕OOO VERY LOW	CRITICAL
Physical function at >3 months (Neck Disability Index, 0-100, high is poor outcome, final score) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	35	33	-	MD 3.6 lower (8.13 lower to 0.93 higher)	⊕⊕OO LOW	CRITICAL
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) (Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 3.3 lower (7.01 lower to 0.41 higher)	⊕⊕OO LOW	CRITICAL
Discontinuation at ≤3 months (follow-up 4-12 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/50 (2%)	4.2%	See comment	43 fewer per 1000 (from 39 fewer to 46 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Discontinuation at >3 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/35 (0%)	5.7%	OR 0.13 (0.01 to 2.14)	49 fewer per 1000 (from 56 fewer to 58 more)	⊕⊕OO LOW	IMPORTANT

1 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
2 Heterogeneity, I^2=61%, p=0.05, unexplained by subgroup analysis.
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence profile: mixed modality manual therapy vs. acupuncture/dry needling

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed modality manual therapy**	**Acupuncture/dry needling**	**Relative (95% CI)**	**Absolute**		
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final score) (follow-up 10 days; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	13	-	MD 5.4 lower (18.3 lower to 7.5 higher)	⊕⊕OO LOW	CRITICAL
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final score) (follow-up 10 days; range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	13	-	MD 2.9 higher (1.22 lower to 7.02 higher)	⊕⊕OO LOW	CRITICAL
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) (follow-up 10 days; range of scores: 0-52; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13	13	-	MD 1.8 higher (2.71 lower to 6.31 higher)	⊕OOO VERY LOW	CRITICAL

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

Table 21: Clinical evidence profile: soft tissue technique vs. acupuncture/dry needling

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Soft tissue technique**	**Acupuncture/dry needling**	**Relative (95% CI)**	**Absolute**		
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) (follow-up 9-28 days; range of scores: 0-100; Better indicated by lower values)												
2	randomised trials	very serious[1]	very serious[2]	no serious indirectness	serious[3]	none	58	57	-	MD 10.19 higher (9.35 lower to 29.73 higher)	⊕OOO VERY LOW	CRITICAL
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values) (follow-up 9 days; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12	12	-	MD 3 higher (1.35 lower to 7.35 higher)	⊕⊕OO LOW	CRITICAL
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) (follow-up 9 days; range of scores: 0-52; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12	12	-	MD 1.8 lower (4.42 lower to 0.82 higher)	⊕OOO VERY LOW	CRITICAL
Discontinuation at ≤3 months (follow-up 2 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	0/47 (0%)	0%	RD 0 (-0.04 to 0.04)	0 more per 1000 (from 40 fewer to 40 more)	⊕⊕⊕O MODERATE	IMPORTANT

1 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
2 Heterogeneity, I^2=50%, p=0.04, unexplained by subgroup analysis
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 22: Clinical evidence profile: manipulation/mobilisation vs. acupuncture/dry needling

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Manipulation/mobilisation**	**Acupuncture/dry needling**	**Relative (95% CI)**	**Absolute**		
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) (follow-up 9 days; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12	12	-	MD 3.9 lower (15.73 lower to 7.93 higher)	⊕OOO VERY LOW	CRITICAL
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values) (follow-up 9 days; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 2.2 lower (6.55 lower to 2.15 higher)	⊕⊕OO LOW	CRITICAL

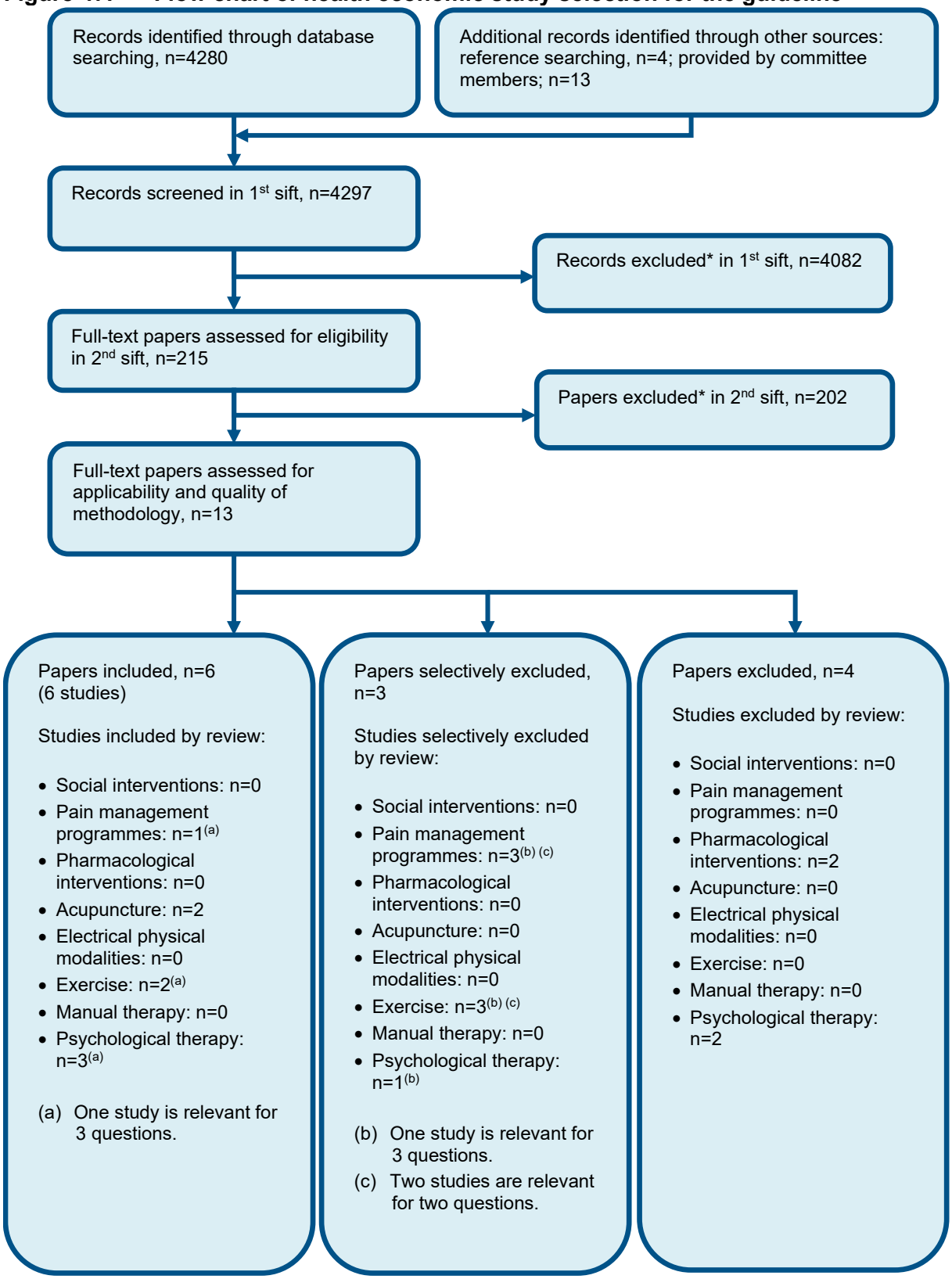
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) (follow-up 9 days; range of scores: 0-52; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 5.1 lower (7.81 to 2.39 lower)	⊕⊕⊕O MODERATE	CRITICAL

1 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

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

Appendix G: Health economic evidence selection

Figure 47: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 23: Studies excluded from the clinical review

Study	Exclusion reason
Acar 2012[1]	Incorrect interventions
Adelizzi 2016[2]	Incorrect interventions. Systematic review
Akhter 2014[3]	Not review population. <3 months pain may be present in some patients
Alam 2018[4]	Not review population. Inappropriate comparison
Aleksiev 2013[6]	Not review population. Inappropriate comparison
Alghadir 2020 [7]	<3 months pain may be present in some patients
Ali 2014[8]	Incorrect study type: Guidance
AlKhadhrawi 2019 [9]	Incorrect interventions
Allan 2003[10]	Inappropriate comparison
Allen 2006[11]	Incorrect study type: Narrative review
Allison 2002[12]	No useable outcomes
Alnigenis 2001[13]	Results not extractable
Amini 2017[14]	<3 months pain may be present in some patients. Not review population
Anderson 2011[15]	Incorrect trial design. Single-arm trial, no comparator
Anonymous 2005[16]	Systematic review too broad
Anonymous 2005[17]	Incorrect study type: Editorial
Anonymous 2016[18]	Incorrect study type: Editorial
Anonymous 2017[19]	Incorrect study type: summary article
Bakar 2014[21]	No relevant outcomes
Bale 2005[22]	Inappropriate comparison. No comparator
Bang 2000[23]	Not review population. Pain not primary
Barbour 2000[24]	Incorrect study type: Questionnaire
Basson 2017[25]	Systematic review too broad
Bautista-aguirre 2017[26]	Inappropriate comparison
Beardsley 2015[27]	Systematic review is not relevant to review question or unclear PICO
Beattie 2010[28]	Incorrect study type: Expert opinion
Behrangrad 2020 [29]	<3 months pain may be present in some patients
Beinert 2015[30]	Incorrect interventions
Beltran-alacreu 2015[31]	Inappropriate comparison
Bernal-Utrera 2019 [32]	Study protocol
Bervoets 2015[33]	Systematic review too broad
Bokarius 2010[35]	Non-Cochrane review
Borman 2008[36]	Inappropriate comparison. Combined interventions
Bracht 2018[37]	Inappropriate comparison
Brantingham 2011[38]	Systematic review is not relevant to review question or unclear PICO
Bron 2007[41]	Study type: Protocol

Bron 2011 [40]	Inappropriate comparison
Bronfort 2001[42]	Inappropriate comparison
Bronfort 2010[43]	Systematic review too broad
Bronfort 2014[44]	Incorrect interventions. Combined interventions
Bryans 2014[45]	Non-Cochrane review
Burckhardt 1992[47]	Abstract
Burckhardt 2002[46]	Study type: Review article
Buttagat 2011[48]	Not review population. Existing NICE guidance: Low back pain
Buttagat 2016[49]	Inappropriate comparison
Canter 2006[51]	Systematic review is not relevant to review question or unclear PICO
Cao 2010[52]	Systematic review is not relevant to review question or unclear PICO
Casanova-mendez 2014[53]	Inappropriate comparison
Castro sanchez 2019[58]	Results not extractable
Castro-sanchez 2011[55]	Inappropriate comparison
Castro-sanchez 2011[56]	Inappropriate comparison
Castro-sanchez 2011[57]	Inappropriate comparison
Castro-sanchez 2014[54]	Data not extractable
Cathcart 2018[59]	Not review population. Healthy participants
Celenay 2016[61]	Not available
Chang 2015[62]	Systematic review too broad
Chen 2014[63]	Systematic review too broad
Cherkin 2003[64]	Systematic review is not relevant to review question or unclear PICO
Chiu 2011[65]	Inappropriate comparison
Clar 2014[66]	Systematic review too broad
Cole 2001[67]	Study type: Editorial
Collado-mateo 2015[68]	Incorrect interventions
Cook 2015[69]	Inappropriate comparison
Coronado 2012[70]	Outcome not in PICO
Costa 2006[71]	Study type: Editorial
Coulter 2019[72]	Non-Cochrane review
Craane 2012[73]	Combined interventions
Cramer 2011[74]	Incorrect interventions
D. farcas 2010[96]	Abstract only
Da silva 2007[76]	Inappropriate comparison
Damgaard 2013[77]	Systematic review too broad
De las penas 2005[78]	Systematic review is not relevant to review question or unclear PICO
De meulemeester 2017[79]	Not review population. <3 months pain may be present in some patients
De oliveira 2018[80]	Single-armed trial
Deepal 2011[243]	Combined interventions
Depintor jidiene 2011[81]	Conference abstract
Devitt 2001[82]	Study type: Editorial
Devocht 2013[83]	Incorrect interventions
Ekici 2009[84]	Inappropriate comparison

Ekici 2017[85]	Inappropriate comparison
El Gendy 2019 [86]	Inappropriate comparison
Erickson 2008[87]	Systematic review is not relevant to review question or unclear PICO
Ernst 2009[88]	Study type: Summary article
Ernst 2009[89]	Systematic review is not relevant to review question or unclear PICO
Ernst 2012[90]	Summary of reviews
Escortell mayor 2008[91]	Inappropriate comparison
Espi-lopez 2018[92]	<3 months pain may be present in some patients. Not review population
Essex 2017[93]	Incorrect interventions
Evans 2002[94]	Combined treatments
Evans 2012[95]	Inappropriate comparison
Feine 1997[97]	Systematic review is not relevant to review question or unclear PICO
Fernandez-de-las-penas 2006[98]	Not review population. <3 months pain may be present in some patients
Fernández-pérez 2008[99]	Not review population. Healthy participants
Field 2002[101]	Inappropriate comparison
Field 2003[100]	Inappropriate comparison
Fitzgerald 2009[102]	Not review population. Pain not primary
Fitzgerald 2013 [103]	Incorrect interventions
Franco 2016[105]	Systematic review is not relevant to review question or unclear PICO
Franco 2017[106]	Systematic review is not relevant to review question or unclear PICO
Franke 2017[108]	Systematic review is not relevant to review question or unclear PICO
Fryer 2005[110]	Incorrect trial design
Fryer 2005[109]	Not review population. <3 months pain may be present in some patients
Fuentes-marquez 2018[111]	Systematic review too broad
Galindez-ibarbengoetxea 2018[112]	Inappropriate comparison
Gamber 2002[113]	Results not extractable
Ganesh 2016[114]	No useable outcomes
Garcia-perez-juana 2018[115]	Inappropriate comparison. Sham manipulation control
Gatchel 2003[116]	Study type: Editorial
Giles 1999[117]	Not review population. Existing NICE guidance: Low back pain
Giles 2003[118]	Existing NICE guidance: Low back pain
Glickman-simon 2013[119]	Summary article
Gordon 2006[120]	Inappropriate comparison
Graham 2008[121]	Systematic review is not relevant to review question or unclear PICO
Groeneweg 2010[122]	Not review population. <3 months pain may be present in some patients
Gross 2015[123]	Systematic review is not relevant to review question or unclear PICO

Gudavalli 2005[124]	Not available
Gudavalli 2015[125]	Inappropriate comparison
Gur 2006[126]	Narrative review
Gusi 2008[128]	Incorrect interventions
Gusi 2010[127]	Incorrect interventions
Hains 2000[131]	Single-armed trial
Hains 2010[130]	Inappropriate comparison
Hains 2015[129]	Incorrect trial design
Haller 2016[132]	Inappropriate comparison
Hanney 2017[133]	Not review population. Healthy participants
Hasson 2004[134]	Inappropriate comparison
Havermark 2006[135]	Incorrect interventions
Hawk 2002[136]	Inappropriate comparison
Hawk 2005[137]	Incorrect interventions
Hawk 2006[138]	Not review population. Existing NICE guidance: Low back pain
Hoeger bement 2011[139]	Incorrect interventions
Hou 2002[140]	Not review population. <3 months pain may be present in some patients
Hurwitz 1996[141]	Systematic review too broad
Irnich 2001[142]	Not review population. Pain not primary. <3 months pain may be present in some patients
Izquierdo perez 2014[143]	Inappropriate comparison. All interventions in same category
Jones 2019 [144]	Inappropriate comparison
Jordan 1998[145]	Inappropriate comparison
Kalamir 2007[148]	Narrative review
Kalamir 2010[147]	Not review population. Pain not primary
Kalamir 2012[146]	No useable outcomes
Kalichman 2010[149]	Narrative review
Keeratitanont 2015[150]	Systematic review is not relevant to review question or unclear PICO
Kemler 2001[153]	Inappropriate comparison. Combined interventions
Kemler 2002[152]	Inappropriate comparison. Combined treatments
Kemler 2008[151]	Incorrect interventions. Economic evaluation
Khalessi 2008[154]	Incorrect interventions
Kim 2019[155]	Incorrect interventions. Inappropriate comparison
Kim 2019 [156]	Study protocol
Klotz 2019[157]	Non-Cochrane review
Knebl 2002[158]	Not review population. Pain not primary
Kraaijenga 2014[159]	Not review population
Kumnerddee 2009[160]	Existing NICE guidance: Low back pain
Laframboise 2016[161]	Inappropriate comparison
Lang 1988[162]	Abstract only
Lau 2011[163]	Incorrect interventions
Lauche 2013[164]	Incorrect interventions
Lauche 2016[165]	Incorrect interventions
Lee 2010[168]	Incorrect interventions
Lee 2013[167]	Incorrect interventions

Lee 2014[169]	No useable outcomes
Leininger 2016[170]	Incorrect interventions
Li 2012[171]	Not guideline condition
Li 2014[172]	Not review population. Pain not primary
Lin 2012[173]	Systematic review too broad
Liptan 2013[175]	Incorrect trial design
Lopez-lopez 2015[177]	Inappropriate comparison
Lund 2006[178]	Incorrect trial design
Martel 2011[180]	Crossover study
Martinez-segura 2012[181]	Inappropriate comparison
Matsubara 2011[182]	Data not extractable
Mohammadi kojidi 2016[183]	Pain not chronic primary
Montenegro 2008[184]	Narrative review
Moraska 2017[185]	Existing NICE guidance: Headache
Moustafa 2015[186]	Incorrect interventions
Moustafa 2018[187]	<3 months pain may be present in some patients
Muir 2000[188]	Narrative review
Muller 2005[189]	Pain not primary
Murphy 2010[191]	Inappropriate comparison
Murphy 2010[190]	Study type: Editorial
Myers 2007[192]	Narrative review
Nasb 2020 [193]	Inappropriate comparison
Nicholson 2000[195]	Letter to editor
Niu 2017[196]	Incorrect interventions
Oerlemans 2000[198]	Inappropriate comparison
Offenbacher 2000[199]	Incorrect interventions
Olah 2008[200]	Incorrect interventions
Oliveira-campelo 2010[202]	Not review population. <3 months pain may be present in some patients
Oliveira-campelo 2013[201]	Not review population. <3 months pain may be present in some patients
O'reilly 1996[197]	<3 months pain may be present in some patients. Not review population
Otis 2009[203]	Incorrect interventions. Not chronic primary pain
Pach 2018[204]	Incorrect interventions
Packer 2014[205]	Inappropriate comparison
Page 2019[206]	Incorrect interventions
Palmgren 2006[207]	Incorrect interventions
Panton 2009[208]	Inappropriate comparison
Paolucci 2016[209]	Incorrect interventions
Peek 2015[210]	Systematic review is not relevant to review question or unclear PICO
Perrot 2014[211]	Systematic review is not relevant to review question or unclear PICO
Petersen 2015[212]	Incorrect interventions
Pico-Espinosa 2020 [213]	Incorrect population (subacute and chronic pain)
Pires 2015[214]	Inappropriate comparison
Pollard 2002[216]	Conference abstract

Pool 2010[217]	<3 months pain may be present in some patients. Not review population
Puntumetakul 2015[219]	Inappropriate comparison
Reis 2014[220]	Inappropriate comparison
Renan-ordine 2011[221]	Pain not primary. Not guideline condition
River 2012[222]	Incorrect trial design
Rodriguez-fuentes 2016[223]	Incorrect interventions
Rogers 1997[224]	Incorrect trial design
Saadat 2018[225]	<3 months pain may be present in some patients
Saavedra-hernandez 2013[226]	Inappropriate comparison
Saban 2014[227]	Inappropriate comparison
Sachdeva 2019 [228]	<3 months pain may be present in some patients
Sadria 2017[229]	Inappropriate comparison
Saha 2017[230]	Incorrect interventions
Salehi 2015[231]	Systematic review is not relevant to review question or unclear PICO
Salom-moreno 2014[232]	Inappropriate comparison
Sanudo 2012[234]	Incorrect interventions
Sanudo 2013[233]	Inappropriate comparison
Sarac 2006[235]	Systematic review is not relevant to review question or unclear PICO
Scholten-peeters 2013[236]	Systematic review is not relevant to review question or unclear PICO
Schulz 2011[237]	Study protocol
Schumacher 2009[238]	Inappropriate comparison
Schwerla 2008[239]	Inappropriate comparison
Seers 2008[240]	Existing NICE guidance: Low back pain
Serrano-aguilar 2011[241]	Cross-sectional study
Severens 1999[242]	No useable outcomes
Sherman 2009[244]	Inappropriate comparison
Shin 2007[246]	Incorrect trial design
Shoskes 2010[247]	Incorrect trial design
Silber 2004[248]	Letter to editor
Sillevis 2010[249]	Inappropriate comparison
Silva 2018[250]	Inappropriate comparison. Sham manipulation control
Simms 1994[251]	Narrative review
Skillgate 2020 [252]	Incorrect population (subacute and chronic)
Sloop 1982[253]	Pain not primary
Smart 2016[254]	Pain not primary
Snodgrass 2014[255]	Inappropriate comparison
Somprasong 2011[257]	Incorrect interventions
Strunk 2008[258]	<3 months pain may be present in some patients
Su 2016[259]	Systematic review is not relevant to review question or unclear PICO
Sunshine 1996[260]	No useable outcomes
Suvarnnato 2013[261]	Inappropriate comparison
Swenson 2003[262]	Narrative review

Taylor 2006[263]	Systematic review is not relevant to review question or unclear PICO
Theadom 2015[264]	Incorrect interventions
Toprak celenay 2017[265]	Incorrect interventions
Townsend 2014[266]	Pain not primary
Trampas 2010[267]	Pain not primary. <3 months pain may be present in some patients
Tse 2010[268]	Inappropriate comparison
Valencia 2009[269]	Inappropriate comparison
Valera-calero 2019[270]	Inappropriate comparison. Sham manipulation control
Van 2000[273]	Abstract only
Van dongen 2015[271]	Abstract only
Van dongen 2016[272]	<3 months pain may be present in some patients
Vas 2014[274]	Incorrect interventions
Vernon 1990[278]	<3 months pain may be present in some patients
Vernon 2007[276]	Systematic review is not relevant to review question or unclear PICO
Vernon 2007[275]	Overview of reviews
Vernon 2009[277]	Systematic review is not relevant to review question or unclear PICO
Vincent 2013[279]	Systematic review is not relevant to review question or unclear PICO
Vitorino 2006[280]	Inappropriate comparison
Walach 2003[281]	Not guideline condition
Wilson 2001[282]	Abstract only
Wise 2002[283]	Conference abstract
Xing 2017[284]	Pain not primary
Yagci 2004[285]	Inappropriate comparison
Yeganeh lari 2016[286]	<3 months pain may be present in some patients
Yildirim 2016[287]	<3 months pain may be present in some patients
Yuan 2015[288]	Systematic review is not relevant to review question or unclear PICO
Yun 2015[289]	Incorrect interventions

I.2 Excluded health economic studies

Studies that meet the review protocol population and interventions, and the economic study inclusion criteria but have not been included in the review based on applicability and/or methodological quality are summarised below with reasons for exclusion.

Table 24: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix J: Research recommendations

J.1 Manual therapy

Research question: What is the clinical and cost effectiveness of manual therapy for managing chronic primary pain in people aged 16 years and over?

Why this is important:

Chronic primary pain is widespread in the population, has high impact on the quality of life of people affected by pain that does not go away. It affects the ability to carry out paid and unpaid work and has consequences for the person in pain, their family and society at large. Manual therapy is one of the treatments people with chronic primary care seek, but little is known about its effectiveness and cost-effectiveness.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People aged >16 years affected by chronic primary pain Intervention(s): Manual therapy: • Soft tissue technique (e.g. massage, muscle energy technique, myofascial/trigger point release) • Traction • Manipulation/mobilisation (including spinal manipulation therapy (SMT) and Maitland technique) • Mixed modality manual therapy (soft tissue technique +/- traction +/- manipulation/mobilisation) Comparison: Passive usual care (being registered with primary care without active treatment or regular pastoral care) Outcome(s): Quality of life, pain severity, function, adverse events
Importance to patients or the population	Chronic primary pain has high prevalence and incidence and affects a large number of people directly and indirectly. Even minor improvements would have high impact on quality of life at large on a population level, therefore determining whether manual therapies can be of benefit to people with chronic pain would be of high importance.
Relevance to NICE guidance	An evaluation of single modality manual therapy for chronic primary pain could inform the composition of multimodal pain management programmes with manual therapy as a component as well as potentially informing a recommendation on single modality manual therapy for future updates of this guideline.
Relevance to the NHS	As manual therapy is operator-dependent and therapist-delivered this would have implications for workforce and training to deliver such hands-on treatments. It is delivered within the NHS at present and therefore guidance on the effectiveness in people with chronic primary pain would be of relevance.
National priorities	The question relates to both loneliness as national priority and the green paper issued by the Department of Health and Social Care in conjunction with the Department for Work and Pensions. One of the potential aims is to help people with chronic primary pain to fulfil their social commitments, which can be paid work or unpaid work, for example informal care work. It has therefore impact on the reduction of loneliness and improvements in quality of life as national priority.
Current evidence base	The evidence review in the guideline revealed a paucity of data for manual therapy, leaving a need to increase the evidence base in order to make informed policy decisions. A recent Cochrane review of manual therapy for chronic pelvic pain provided no relevant evidence for manual therapy as monotherapy for pelvic pain. Data in other realms of chronic primary pain are missing, hence the suggestion to research this area.

Equality	As chronic primary pain is more prevalent in socially disadvantaged and marginalised group this research addresses equality issues.
Study design	RCT with either attention control as control group or cluster-randomised RCT differentiating clusters with manual therapy provision for people with chronic primary pain and clusters without. This would allow for health services interventions that put manual therapy in the context of service provision for people with chronic primary pain, who often have associated multiple morbidities including mental health problems. Long term follow up is required to demonstrate effectiveness beyond the duration of the intervention.
Feasibility	A meaningful study at large scale would have huge consequences for funding, practice training (if cluster randomised RCT) and “whole systems” integration.
Other comments	There are important issues to consider: • The research proposal aims to explore monotherapy for a complex common condition. Whilst this is laudable in order to quantify the treatment effect for a single modality treatment this treatment modality is often used alongside other treatment components. This means that such a study should be embedded in a complex interventions framework. • Hands-on treatments are, like talking therapies, operator-dependent (“practitioner-effect”). For pragmatic reasons, presumed specific and non-specific or contextual effects have to be taken into account. • Manual therapies are based on tactile encounters. Touch as communication modality is multi-layered. Its range of effects covers the whole spectrum from power-dependent violation of boundaries to healing, the “laying on hands”. There is a body of research around for the effects of touch, but this stems from nursing literature and palliative care (touch as embodied act of caregiving). • Manual therapy as therapy addressing biomechanical tissue qualities is based on assumptions/sensory perceptions of peripheral nociceptive changes in the tissues. However, chronic primary pain is characterised by the absence of peripheral identifiable nociceptors. This challenges the assumption of delivering a therapy aimed at the peripheral nervous system for a condition affecting predominantly the central nervous system. • It is suggested that manual therapies may have differing efficacy in different types of chronic primary pain, therefore suggest that these are sub-grouped within the research in able to determine any differential efficacy.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

Appendices

Appendix K: MIDs for continuous outcomes

Table 25: MIDs for continuous outcomes (0.5 x SD): mixed modality manual therapy vs. usual care

Outcomes	MID
Pain reduction at ≤3 months (BPI; VAS 0-10, final values and change scores) Scale from: 0 to 10.	1.16
Pain reduction at >3 months (BPI, 0-10, final scores, high scores are poor outcome) Scale from: 0 to 10.	0.95
Physical function at ≤3 months (Oswestry Disability Index, 0-100, change scores and final scores, high is poor outcome) Scale from: 0 to 100.	7.06
Physical function at >3 months (Oswestry Disability Index, 0-100, final scores, high is poor outcome) Scale from: 0 to 100.	5.94
Pain interference at ≤3 months (BPI – interference, 0-10, final scores, high is poor outcome) Scale from: 0-10.	1.52
Pain interference at >3 months (BPI – interference, 0-10, final scores, high is poor outcome) Scale from: 0-10.	0.76

Table 26: MIDs for continuous outcomes (0.5 x SD): soft tissue technique vs. usual care

Outcomes	MID
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values and change scores) Scale from: 0 to 100.	7.28
Health related quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	8.17
Health related quality of life at ≤3 months (SF-12 Mental health, 0-100, high is good outcome, change score) Scale from: 0 to 100.	14
Health related quality of life at >3 months (FIQ, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	3.71
Physical function at ≤3 months (Disability Rating Index, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	8.73

Outcomes	MID
Physical function at ≤3 months (Neck Disability Index, 0-50, high is poor outcome, change scores) Scale from: 0 to 50.	2.49
Psychological distress at ≤3 months (HADS depression subscale, 0-21, high is poor outcome, final score) Scale from: 0 to 21.	2
Psychological distress at ≤3 months (HADS anxiety subscale, 0-21, high is poor outcome, final score) Scale from: 0 to 21.	2.15
Psychological distress at ≤3 months (Perceived Stress Scale, 0-40, high is poor outcome, change scores) Scale from: 0 to 40.	3.11
Sleep disturbance at ≤3 months (mean value for 10 questions about sleep, 0-5, high is poor outcome, final score) Scale from: 0 to 5.	0.35

Table 27: MIDs for continuous outcomes (0.5 x SD): manipulation/mobilisation vs. usual care

Outcomes	MID
Pain reduction at ≤3 months (final values) VAS 0-10. Scale from: 0 to 10.	0.95
Quality of life at ≤3 months (final values) FIQ . Scale from: 0 to 100.	8.15

Table 28: MIDs for continuous outcomes (0.5 x SD): mixed modality manual therapy vs. soft tissue technique

Outcomes	MID
Pain reduction at ≤3 months (NRS, 0-10, high is poor outcome, final score) Scale from: 0 to 10.	0.8
Pain reduction at >3 months (NRS, 0-10, high is poor outcome, final score) Scale from: 0 to 10.	1.13

Table 29: MIDs for continuous outcomes (0.5 x SD): mixed modality manual therapy vs. manipulation/mobilisation

Outcomes	MID
Pain reduction at ≤3 months (pain at rest on VAS, 0-100, final scores, high is poor outcome) Scale from: 0 to 100.	6.19

Table 30: MIDs for continuous outcomes (0.5 x SD): manipulation/mobilisation vs. soft tissue technique

Outcomes	MID
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values and change scores) Scale from: 0 to 100.	9.71
Pain reduction at >3 months (pain reduction on VAS, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	11
Health related quality of life at ≤3 months (SF-12 Physical component, 0-100, high is good outcome, final values and change scores) Scale from: 0 to 100.	5.25
Health related quality of life at ≤3 months (SF-12 Mental component, 0-100, high is good outcome, final values and change scores) Scale from: 0 to 100.	4.25
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values)	4.02
Physical function at >3 months (Neck Disability Index, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	5
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values)	2.28

Table 31: MIDs for continuous outcomes (0.5 x SD): mixed modality manual therapy vs. acupuncture/dry needling

Outcomes	MID
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	10.05
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final score) Scale from: 0 to 100.	1.95
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) Scale from: 0 to 52.	2.45

Table 32: MIDs for continuous outcomes (0.5 x SD): soft tissue technique vs. acupuncture/dry needling

Outcomes	MID
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) Scale from: 0 to 100.	14.25
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values) Scale from: 0 to 100.	2.68

Outcomes	MID
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) Scale from: 0 to 52.	0.41

Table 33: MIDs for continuous outcomes (0.5 x SD): manipulation/mobilisation vs. acupuncture/dry needling

Outcomes	MID
Pain reduction at ≤3 months (pain on VAS, 0-100, high is poor outcome, final values) Scale from: 0 to 100.	7.4
Physical function at ≤3 months (Neck Disability Index, 0-100, high is poor outcome, final values) Scale from: 0 to 100.	2.68
Psychological distress at ≤3 months (Pain Catastrophizing Scale, 0-52, high is poor outcome, final values) Scale from: 0 to 52.	0.41