COST-EFFECTIVENESS OF MANUAL THERAPY FOR THE MANAGEMENT OF MUSCULOSKELETAL CONDITIONS: A SYSTEMATIC REVIEW AND NARRATIVE SYNTHESIS OF EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Objectives: The purpose of this study was to systematically review trial-based economic evaluations of manual therapy relative to other alternative interventions used for the management of musculoskeletal conditions.

Methods: A comprehensive literature search was undertaken in major medical, health-related, science and health economic electronic databases.

Results: Twenty-five publications were included (11 trial-based economic evaluations). The studies compared cost-effectiveness and/or cost-utility of manual therapy interventions to other treatment alternatives in reducing pain (spinal, shoulder, ankle). Manual therapy techniques (eg, osteopathic spinal manipulation, physiotherapy manipulation and mobilization techniques, and chiropractic manipulation with or without other treatments) were more cost-effective than usual general practitioner (GP) care alone or with exercise, spinal stabilization, GP advice, advice to remain active, or brief pain management for improving low back and shoulder pain/disability. Chiropractic manipulation was found to be less costly and more effective than alternative treatment compared with either physiotherapy or GP care in improving neck pain.

Conclusions: Preliminary evidence from this review shows some economic advantage of manual therapy relative to other interventions used for the management of musculoskeletal conditions, indicating that some manual therapy techniques may be more cost-effective than usual GP care, spinal stabilization, GP advice, advice to remain active, or brief pain management for improving low back and shoulder pain/disability. However, at present, there is a paucity of evidence on the cost-effectiveness and/or cost-utility evaluations for manual therapy interventions. Further improvements in the methodological conduct and reporting quality of economic evaluations of manual therapy are warranted in order to facilitate adequate evidence-based decisions among policy makers, health care practitioners, and patients. (J Manipulative Physiol Ther 2014;37:343-362)

Key Indexing Terms: *Cost-Effectiveness; Cost-Utility; Manual Therapy; Systematic Review; Back Pain; Chiropractic*

Manual therapy is a skilled nonsurgical conservative management using the practitioner's hands and/or fingers on the patient's body for the purpose of assessing, diagnosing, and treating a variety of symptoms and conditions.[1,2] Manual therapy is used within the traditional medical (eg, physiotherapy, orthopedics, and

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sports medicine) and complementary and alternative medicine context (eg, chiropractic and osteopathy) and consists of different techniques (eg, manipulation, mobilization, static stretching, and muscle energy techniques). The definition and purpose of manual therapy vary across health care professionals.

The use of manipulation and mobilization has been recommended in clinical practice guidelines in the United States, Great Britain, Canada, and the Netherlands.[3–9] Although past research evidence on the clinical effectiveness [10–19] and safety [20–27] of manual therapy relative to other interventions is abundant, the evidence on cost-effectiveness is insufficient and inconclusive.[28–36] Moreover, to our best knowledge, a systematic review of full economic evaluations of recent evidence (ie, cost-effectiveness [CEA] and/or cost-utility analysis [CUA]) alongside randomized controlled trials (RCTs) of manual therapy has not been conducted.

In light of limited health care resources, policy makers, health care providers, and researchers need to make informed decisions in prioritizing and allocating resources to the provision of health care interventions that are both effective and cost saving. Ideally, the decision-making process should be based on high-quality evidence summarizing incremental costs and effects of a health care intervention of interest compared with alternative interventions.

The aim of this review was to systematically identify, appraise, and evaluate the evidence on trial-based economic evaluations (cost-effectiveness and/or cost-utility) of manual therapy relative to other alternative interventions used for the management of musculoskeletal conditions.

Methods

This review is part of a large technical report of comparative benefits and harms of manual therapy interventions for the management of musculoskeletal and nonmusculoskeletal conditions, commissioned by the Royal College of Chiropractors in the United Kingdom (http://www2.warwick.ac.uk/fac/med/research/hscience/pet/reportforcollegeofchiropractors/).

A comprehensive literature search was undertaken as part of a wider search for this report. The following medical, health-related, science and health economic electronic databases were searched (through August 2011): MEDLINE (Ovid), Embase, Mantis, Index to Chiropractic Literature, CINAHL, Cochrane Airways Group trial register, Cochrane Complementary Medicine Field register, and Cochrane Rehabilitation Field register (via CENTRAL), Science Citation Index, AMED, CDSR, National Health Service (NHS) DARE, NHS HTA, NHS EED, CENTRAL, ASSIA, and Social Science Citation Index. The search strategy used in MEDLINE is provided in Appendix 1. Search terms were restricted to subject heading and free-text terms related to manual therapy. Broader terms such as "physiotherapy" were not included because initial tests suggested that the volume of the literature identified using such a broad search strategy would not be manageable. To keep the search as open as possible, no condition terms were included. The search was limited to the study types included in the wider report by the use of recognized search filters, including the NHS Centre for Reviews and Dissemination NHS EED filter (see: http://www.crd.york.ac.uk/). This performance of this filter has been tested.[37] No date limits were applied. The search results were updated on February 15, 2013. Additional studies were sought through references of relevant primary studies and systematic reviews.

This review included English-language full-text publications of RCTs that evaluated the cost-effectiveness and/or cost-utility of manual therapy (eg, manipulation, mobilization, static stretching, chiropractic care, muscle energy techniques alone or in combination) compared with alternative interventions (eg, no treatment, placebo, and usual care) used for the management of musculoskeletal conditions. We defined *musculoskeletal conditions* as disorders of muscles, nerves, tendons, ligaments, joints, cartilage, and spinal disks that develop over time. They can be categorized as spinal (eg, mid, low back or neck pain, sciatica, and headaches), upper extremity (eg, shoulder disorders, carpal tunnel syndrome, and lateral epicondylitis), and lower extremity (eg, ankle sprain) disorders.

We excluded studies where manual therapy was used to treat acute injuries such as fractures and dislocations (eg, to realign bones), except when used for rehabilitation purposes. Studies reporting only costs, only outcomes, reviews, protocols, and conference abstracts were excluded. Cost-consequence studies were excluded because they present an array of different outcomes and cost measures. Studies for which there was insufficient information to calculate the incremental cost-effectiveness ratios (ICERs) for CEA or CUA were also excluded.

Two independent reviewers (A.T. and P.S.) screened all identified bibliographic records for title/abstract and then for full text. Any disagreements were resolved through consensus or by recourse to a third-party reviewer (A.C.). The first author independently extracted relevant data from included studies which was checked by another reviewer (P.S). The extracted data included study characteristics (eg, author name, country, year of publication, sample size, and follow-up duration), types of participants (eg, condition, age, and sex), types of interventions/comparators, type of economic analysis (cost-effectiveness, cost-utility), perspective (societal, health care system, individual), study currency, discounting, and information pertinent to risk of bias (ROB)/study quality assessment items. The outcomes included pain/disability scores, quality of life (QOL) measures, quality-adjusted life-years (QALYs), costs, and ICERs. We converted mean costs to UK £2012 prices using country-specific gross domestic product deflators[38] and Purchasing Power Parities from Organisation for Economic Co-operation and Development (£1 = US $1.45 in 2012 prices).[39] We calculated ICERs for each study, if not

reported directly. We chose a single willingness to pay (WTP) threshold of £20 000 to £30 000, which is currently used for the National Institute for Health and Care Excellence (NICE).

The methodological and reporting quality of economic analyses of the included studies were assessed using the Drummond 10-item checklist.[40] This tool helps to assess the following domains: (*a*) adequacy of research question, (*b*) description of treatments, (*c*) identification of costs and consequences, (*d*) measurement of costs and consequences, (*e*) valuation and adjustment of costs and consequences for different timing, (*f*) incremental analysis of costs and consequences of alternative treatments, (*g*) uncertainty in the estimates of costs and consequences, and (*g*) presentation and discussion of study results and issues of concern.

The ROB in relation to clinical outcomes (ie, pain and health-related QOL measures) was assessed using the 11-item checklist of internal validity criteria recommended by the Cochrane Back Review Group.[41] This tool is designed to assess the following domains of bias per each outcome: (*a*) selection bias (ie, methods of randomization and allocation concealment, similarity of groups in important prognostic factors at baseline), (*b*) performance bias (ie, blinding of patients and care providers, similarity of cointerventions across study groups), detection bias (ie, blinding of outcome assessors), and attrition bias (ie, noncompliance, dropouts, and intention-to-treat analysis). Based on the number of satisfied criteria (response: yes), the studies were assigned a low (at least 6 criteria satisfied) or a high (5 or fewer criteria satisfied) ROB. This threshold was selected given the empirical evidence showing that trials satisfying at least 6 criteria reported smaller effect sizes than trials satisfying fewer criteria (5 or less).[42] In support of this construct, the previous research has demonstrated that studies of low methodological quality (ie, higher ROB) tend to exaggerate the treatment effects.[43,44]

The results were organized by condition and, within each condition, by type of manual therapy. The results were summarized in text and tables.

Results

We initially identified 25 539 (16 976 after de-duplication) bibliographic records, of which 1014 were included in the technical report through the 2-stage screening process (abstract/title and full text). The updated search contributed additional 229 potentially relevant records. Thus, a total of 1243 records were screened for the cost-effectiveness review, of which 129 passed at title/abstract screening level and were judged to be potentially relevant for full-text review. One hundred four of the 129 publications were excluded at full text (these included studies that reported information on costs [n = 31] or outcomes [n = 3] only, cost-consequence studies [n = 9], and CUAs where not enough information was provided to calculate the ICER [n = 2]). Figure 1 provides full details of the search results and reasons for exclusion. The remaining 25 publications, representing 11 unique RCTs included in the review, were the following: Bosmans et al,[45–47] Williams et al,[48,49] the UK Back Pain Exercise and Manipulation (BEAM) trial team 2004,[50–52] Niemisto et al,[53,54] Rivero-Arias et al,[55,56] Bergman et al,[57–60] Whitehurst et al,[61,62] Korthals-de Bos et al,[63,64] Lewis et al,[65,66] Lin et al,[67,68] and Critchley et al.[69]

The study, participant, treatment, methodology, and outcome characteristics for the 11 included trials are presented in Table 1. The studies were conducted in the United Kingdom,[48,50,55,61,65,69] the Netherlands,[45,57,63] Finland,[53] and Australia.[67] The sample size ranged from 94 [67] to 1334 participants.[50] Duration of follow-up ranged from 6 [48,57,65,67] to 24 months.[53] The mean age of participants ranged from 37[53] to 51 years.[65] The participants presented with spinal pain (low/upper back, neck),[48] low back pain,[50,53,55,61,69] neck pain,[45,63,65] shoulder pain,[57] and ankle fractures.[67] Most studies included participants with nonspecific pain (ie, patients with spinal/shoulder pathology, rheumatoid arthritis, malignancies, pregnancy, osteoarthritis, psychiatric disease, or herniated disk were excluded). In the reviewed studies, interventions whose main components included manual therapy techniques (eg, manipulation and mobilization) were compared with usual general practitioner (GP) care,[48,50,57,63] GP advice,[53] physiotherapist advice,[55] pain management program (back pain education, strengthening, stretching, aerobic exercise),[61,69] exercise,[45] physiotherapy (postural relaxation, walking exercises),[63,67] or advice and exercise (A&E).[65] Most interventions lasted from 6 to 12 weeks. The cost-effectiveness analyses were based on pain intensity and disability measures. The utility for QALY was based on the EuroQoL EQ-5D (European Quality of Life–5 Dimensions) or the Assessment of Quality of Life (AQoL). The perspective of economic evaluations was societal [45,53,55,57,63,65] or health care system.[48,50,55,61,65,67,69] All studies from a societal perspective included direct medical, direct nonmedical, and indirect costs. Given 12 months of follow-up in most studies, no discounting was undertaken (see Table 1).

Methodological and Reporting Quality of Economic Evaluations

The quality assessment showing the percentage of items with "yes" on the Drummond checklist is presented in Table 2. In all studies, the research question was clearly formulated, with good descriptions of the interventions and comparators. Most studies reported all important costs (ie, direct medical, direct nonmedical, and indirect) and consequences (ie, outcome measures). Because costs were not individually itemized for more than half of the studies, it was not clear what data were

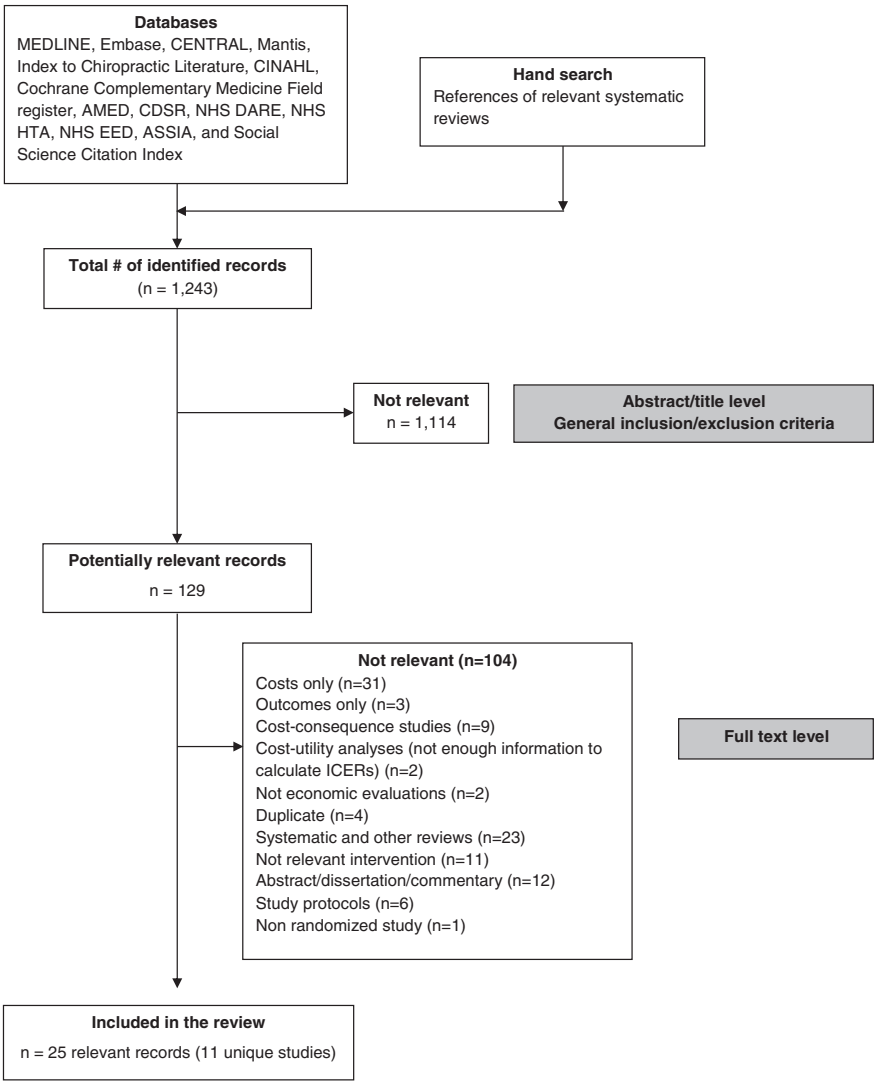

Fig 1. *Flowchart of the study selection process.*

used to calculate the total costs. All studies reported valuation methods of costs and consequences, which were judged as adequate. The ICERs were reported in all studies, except for 1 study where information was provided to calculate this ratio.[67,68] The studies provided detailed discussion sections by highlighting main study findings, interpretation of the findings, study strengths and limitations, consistency of findings with other studies, and future directions.

Risk of Bias Assessment

Risk of bias assessments are presented in Table 3. Briefly, 7 of the 11 included trials were rated as having low ROB [45,50,53,57,61,67,69] and 4 trials as having high ROB.[48,55,63,65] Patients and care providers in the studies were not blinded to the intervention type, and because the outcomes were self-reported (eg, pain, QOL), blinding of assessors was considered not applicable. Most of the studies reported adequate methods of randomization and treatment allocation concealment. Results of all studies were based on intention-to-treat analysis.

Cost-Effectiveness and/or Cost-Utility of Manual Therapy

Results are presented by condition in the text below as well as in Table 4.

Spinal Pain (Low Back, Upper Back, and/or Neck). In a trial by Williams et al[48,49] the addition of osteopathic manipulation to usual GP care was more costly compared with

Table 1. *Included RCTs and Their Characteristics*

Study ID	Study Participants Eligibility Criteria	Study Perspective Type of Costs Methods	Interventions (Components)	Outcome Measures Follow-up
Spinal (upper/low back, neck, or both) pain				
Williams 2004 [48,49] UK	**Sample size:** 201 patients (randomised), 136 patients (analysed) **Age (mean):** NR **Male (%):** NR **Inclusion:** patients aged 16-65 years with non-specific neck or back pain for 2-12 weeks **Exclusion:** patients with serious spinal pathology, nerve root pain, previous spinal surgery, or major psychological disorder	**Perspective:** National Health Service **Direct medical costs**: GP and outpatient consultations, investigations, prescribing, hospital stay **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: None (study duration < 1 year)	**Intervention 1:** OSM (osteopathic manipulation + advice on keeping active, exercise regularly, and avoiding excessive rest) + Usual GP care [3-4 sessions] **Intervention 2:** Usual GP care [3-4 sessions] **Duration:** 2 months	Mean QALY (based on quality of life score EuroQoL EQ-5D) ICER **Last follow-up:** 6 months
Low Back Pain				
Critchley 2007 [69] UK	**Sample size:** 212 patients (randomised), 148 patients (analysed) **Age (mean):** 44 years **Male (%):** 50 **Inclusion:** patients aged ≥18 years referred by GP with non-specific LBP >12 weeks **Exclusion:** previous spinal surgery, PT for LBP within 6 months prior to enrolment, chronic conditions such as rheumatoid arthritis or disabilities rendering unsuitable for the treatment	**Perspective:** National Health Service **Direct medical costs**: Hospital stays and visits, staff time, procedures, investigations **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: 3.5%	**Intervention 1:** Individual PT (joint manipulation, mobilisation, massage, back care advice, individual exercises including trunk muscle retraining, stretches, and general spinal mobility) [12 sessions] **Intervention 2:** spinal stabilisation PT (transverses abdominis and lumbar multifidus muscle training, exercise for spinal stability) [8 sessions] **Intervention 3:** Pain management (back pain education, strengthening, stretching, aerobic exercise, cognitive behavioural approach) [8 sessions] **Duration:** NR	Mean QALY (based on quality of life score EuroQoL EQ-5D) ICER **Last follow-up:** 18 months
Niemisto 2005 [53,54] Finland	**Sample size:** 204 patients (randomised), 138 patients (analysed) **Age (mean):** 37 years **Male (%):** 46 **Inclusion:** patients 24-46 years of age with non-specific LBP ≥ 3 months and disability measured with ODI of 16% **Exclusion:** malignancies, ankylosing spondylitis, severe osteoporosis, osteoarthritis, paralysis, progressive neurologic disorder, haemophilia, spinal infection, spinal operation, vertebral fracture within 6 months of trial, pregnancy, severe sciatica, and psychiatric disease	**Perspective:** Societal **Direct medical costs**: Physician visits, physiotherapy visits, outpatient clinics, hospital stays, x-rays **Direct non-medical costs:** Drug and travel costs **Indirect costs:** Productivity loss costs **Discounting**: None	**Intervention 1:** Manipulative combination treatment (manipulation with muscle energy technique to correct any biomechanical dysfunction in the lumbar or pelvic segments, stabilizing exercise to correct the lumbopelvic rhythm, GP advice) [4 sessions] **Intervention 2:** GP advice (booklet, advice on exercise, muscle stretch, and stability) [1 session] **Duration:** 4 weeks	ICER (based on pain and ODI scores) **Last follow-up:** 24 months

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Table 1. (*continued*)

Study ID	Study Participants Eligibility Criteria	Study Perspective Type of Costs Methods	Interventions (Components)	Outcome Measures Follow-up
Rivero-Arias 2006 [55,56] UK	**Sample size:** 286 patients (randomised and analysed) **Age (mean):** 41 years **Male (%):** 47.5 **Inclusion:** patients ≥18 years with LBP ≥ 6 weeks **Exclusion:** patients with systemic rheumatologic disease, gynaecological problems, ankylosing spondylitis, tumours, infections, past spinal surgery, or treatment for physical problems	**Perspective:** National Health Service and Societal **Direct medical costs**: NHS costs (intervention, GP visits, hospitalisations, prescribed items) **Direct non-medical costs:** Health care purchased by patient (private consultations with osteopaths, chiropractors, over the counter drugs) **Indirect costs:** employment costs (number of days off work) **Discounting**: None (12 months follow-up)	**Intervention 1:** PT (joint manipulation, mobilisation, massage, stretching, spinal mobility and strengthening exercise, heat/cold therapy) + advice to remain active (back book) [5 sessions] **Intervention 2:** Advice to remain active (back book) [1 session] **Duration:** NR	Mean QALY (based on quality of life score EuroQoL EQ-5D) ICER **Last follow-up:** 12 months
UK BEAM 2004 [50–52] UK	**Sample size:** 1334 patients (randomised), 1287 patients (analysed) **Age (mean):** 43.1 years **Male (%):** 44 **Inclusion:** patients 18-65 years of age with non-specific LBP ≥ 1 months and RMDQ ≥ 4 **Exclusion:** patients with malignancies, ankylosing spondylitis, osteoporosis, infections, past spinal surgery, psychiatric disease, treatment for physical problems 3 months before trial, chronic use of steroids, cardiovascular condition, or previous attendance to pain management clinic	**Perspective:** National Health Service **Direct medical costs**: GP care/consultations, visits, outpatient attendance, hospital stay, programmes of exercise, manipulation **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: None (12 months follow-up)	**Intervention 1:** GP care **Intervention 2:** Exercise + GP care [9 sessions] **Intervention 3:** Manipulation (a multidisciplinary group developed a package of techniques representative of those used by the UK chiropractic, osteopathic, and physiotherapy professions) + GP care [9 sessions] **Intervention 4:** Manipulation + exercise + GP care [9 sessions] **Duration:** 12 weeks	Mean QALY (based on quality of life score EuroQoL EQ-5D) ICER **Last follow-up:** 12 months
Whitehurst 2007 [61,62] UK	**Sample size:** 402 patients (randomised and analysed) **Age (mean):** 41 years **Male (%):** 47 **Inclusion:** patients 18-64 years of age with non-specific LBP < 12 weeks **Exclusion:** serious spinal or systemic disorders, long-term sick leave (> 12 weeks), osteoporosis, inflammatory arthritis, steroid treatment (> 12 weeks), pregnancy, previous hip/back surgery or fracture, abdominal surgery, back pain treatment by another professional	**Perspective:** National Health Service **Direct medical costs**: |treatment sessions (PT and |BPM), outpatient attendance, inpatient attendance, primary care contacts, other health professionals (e.g., acupuncture, chiropractic, osteopathy, physiotherapy) **Direct non-medical costs:** NA **Indirect costs:** NA **Discounting**: None (12 months follow-up)	**Intervention 1:** Manual PT (articulatory mobilisation, manipulation, or soft tissue techniques, spinal stabilisation, back exercise, ergonomic advice, back education) [7 sessions] **Intervention 2:** BPM (general fitness, exercise for spinal mobility, explanation about pain mechanisms, distress, coping strategies) [2-day course plus clinical tutoring] **Duration:** NR	Mean QALY ICER (based on EuroQoL EQ-5D; RMDQ score) Last follow-up: 12 months
Neck Pain				
Bosmans 2011 [45–47] The Netherlands	**Sample size:** 146 patients (randomised and analysed) **Age (mean):** 45 years **Male (%):** 40	**Perspective:** Societal **Direct medical costs**: Primary care (GP, SMT, BGA, massage,	**Intervention 1:** SMT (manipulation using passive movement of a joint beyond its active and passive limit	Mean QALY ICER (based on mean QALY; pain; perceived recovery; NDI)

Table 1. (*continued*)

Study ID	Study Participants Eligibility Criteria	Study Perspective Type of Costs Methods	Interventions (Components)	Outcome Measures Follow-up
	Inclusion: patients 18-70 years of age with non-specific neck pain (4-12 weeks) **Exclusion:** malignancy, neurologic disease, herniated disc, or systemic rheumatic disease	homeopathy, outpatient visit, x-ray, tomography, MRI), supportive care **Direct non-medical costs:** Informal care, paid home help **Indirect costs:** Absenteeism from paid/unpaid work **Discounting**: None (12 months follow-up)	of motion with a localized thrust of small amplitude to regain motion, restore function, and reduce pain; mobilisation using skilled low grade passive movement with large amplitude to restore movement and relieve pain) [6 sessions] **Intervention 2:** BGA (gradually increasing exercise program) [18 sessions] **Duration:** 6 weeks	**Last follow-up:** 12 months
Korthals-de Bos 2003 [63,64] The Netherlands	**Sample size:** 183 patients (randomised), 178 patients (analysed) **Age (mean):** 45 years **Male (%):** 40 **Inclusion:** patients 18-70 years of age with non-specific neck pain (≥ 2 weeks) **Exclusion:** previous neck surgery, malignancy, neurologic disease, fracture, herniated disc, or systemic rheumatic disease	**Perspective:** Societal **Direct medical costs**: GP, SMT, PT, outpatient appointments, hospitalisation, exercise, home care **Direct non-medical costs:** Alternative therapy, home care, friend's or partner's help, travel **Indirect costs:** Absenteeism from paid/unpaid work **Discounting**: None (trial duration: 12 months)	**Intervention 1:** SMT (combination of techniques described by Cyeariax, Kaltenborn, Maitland, and Mennel using hands-on muscular and articular mobilisation techniques, coordination or stabilisation techniques, and joint mobilisation with low-velocity passive movements) [6 sessions] **Intervention 2:** PT (active, postural, or relaxation exercises, stretching, massage, manual traction) [12 sessions] **Intervention 3:** GP care (standard care, advice on self-care, education, ergonomic issues, paracetamol or NSAIDs, if necessary) [1 session and optional biweekly follow-up visits] **Duration:** 6 weeks	Mean QALY ICER (based on EuroQoL EQ-5D; pain; NDI) **Last follow-up:** 12 months
Lewis 2007 [65,66] UK	**Sample size:** 350 patients (randomised), 346 patients (analysed) **Age (mean):** 51 years **Male (%):** 37 **Inclusion:** patients ≥ 18 years with non-specific neck pain who consulted only primary care team in the previous 6 months **Exclusion:** weight loss, fever, progressive neurologic signs, muscle weakness, sensation disturbance, malignancy, systemic rheumatic disease, osteoporosis, contraindications to the	**Perspective:** National Health Service and Societal **Direct medical costs**: Study intervention sessions, GP consultations, outpatient attendance (e.g., rheumatology, physiotherapist, neurologist, emergency, radiographer, acupuncturist) **Direct non-medical costs:** patient expenses (e.g., prescription drugs, over-the-counter medicines, devices) **Indirect costs:** Absenteeism from paid work **Discounting**: None (trial duration: 6 months	**Intervention 1:** A & E [8 sessions] **Intervention 2:** A & E + SMT (passive/active assisted hands-on movements, joint and soft tissue mobilisations or manipulations graded as appropriate to the patient's signs and symptoms) [8 sessions] **Intervention 3:** A & E + PSWD [8 sessions] **Duration:** 6 weeks	Mean QALY ICER (based on EuroQoL EQ-5D; NPQ) **Last follow-up:** 6 months

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Table 1. (*continued*)

Study ID	Study Participants Eligibility Criteria	Study Perspective Type of Costs Methods	Interventions (Components)	Outcome Measures Follow-up
	study treatments, taking anticoagulants			
Shoulder Pain				
Bergman 2010 [57–60] The Netherlands	**Sample size:** 150 patients (randomised), 140 patients (analysed; excluding 2 outliers) **Age (mean):** 48 years **Male (%):** 49 **Inclusion:** patients ≥ 18 years with non-specific shoulder pain without shoulder treatment in the past 3 months **Exclusion:** fractures, ruptures or dislocations in the shoulder region, previous orthopaedic surgery, contraindications for manipulative therapy, cervical nerve root compression, rheumatic disorder, dementia, psychiatric disorder, or abdominal pathology	**Perspective:** Societal **Direct medical costs**: treatment by GP, physiotherapist, manual, occupational, exercise or complementary health therapists, visits to consultant in orthopedic surgery, acupuncturist, neurology, rheumatology, rehabilitation medicine, and hospitalisation **Direct non-medical costs:** out-of-pocket expenses, costs for paid/unpaid help **Indirect costs:** loss of production due to sick leave from paid/unpaid work **Discounting**: None (trial duration: 6 months)	**Intervention 1:** SMT (high velocity low amplitude manipulation and passive low velocity mobilisation within the range of joint motion) [6 sessions] + Usual GP care (advice on daily living, if needed analgesics, NSAIDs, corticosteroid injections, or PT including massage and exercise) **Intervention 2:** Usual GP care [number sessions: NR] **Duration:** 12 weeks	ICER (based on perceived recovery; shoulder pain; shoulder disability; general health) **Last follow-up:** 6 months
Ankle Fracture				
Lin 2008 [67,68] Australia	**Sample size:** 94 patients (randomised), 92 patients (analysed) **Age (mean):** 41.5 years **Male (%):** 54 **Inclusion:** patients ≥ 18 years with ankle fractures treated with cast immobilisation with cast removed the week before the trial entry, pain VAS ≥ 2, approved to weight-bear as tolerated or partial weight-bear **Exclusion:** patients with significant pathologies	**Perspective:** Health care system and patient **Direct medical costs**: outpatient physiotherapy, medical specialists, GP, emergency department, hospitalisation, medication, investigations, private health providers, **Direct non-medical costs:** public transport, private vehicle **Indirect costs:** None **Discounting**: None (trial duration: 6 months)	**Intervention 1:** MT (large amplitude oscillatory anterior-posterior glides of the talus) + PT (exercise, gait retraining, walking aids, advice, ice, elevation and progression if required) [8 sessions] **Intervention 2:** PT [5 sessions] **Duration:** 4 weeks	ICER (quality of life AQol: QALY) **Last follow-up:** 6 months

A&E, advice and exercise; *BGA*, behavioral graded activity; *BPM*, brief pain management; *EQ-5D*, European Quality of Life-5 Dimensions; *GP*, general practitioner; *ICER*, incremental cost-effectiveness ratio; *LBP*, lower back pain; *MRI*, magnetic resonance imaging; *MT*, manual therapy; *NA*, not applicable; *NDI*, Neck Disability Index; *NHS*, National Health Service; *NPQ*, Northwick Park Neck Pain Questionnaire; *NR*, not reported; *NS*, statistically nonsignificant; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *ODI*, Oswestry Disability Index; *OSM*, osteopathic manual therapy; *PSWD*, pulsed shortwave diathermy; *PT*, physiotherapy/physical therapy; *QALY*, quality-adjusted life year; *RMDQ*, Roland-Morris Disability Questionnaire; *SMT*, spinal manual therapy.

GP care alone (£402 vs £286). The associated ICER was £4674 per QALY gained. This estimate was lower than the threshold of £30 000 used by the NICE, suggesting the addition of osteopathic manipulation to usual GP care as a potentially cost-effective option for patients with spinal pain.

Low Back Pain. In the study by Critchley et al,[69] pain management dominated both individual physiotherapy and spinal stabilization physiotherapy. Individual physiotherapy was more effective and marginally more costly than spinal stabilization physiotherapy, with a mean ICER of £1279 per QALY gained.

Table 2. *Methodological Quality of Economic Evaluations in the Included Studies (the Drummond Checklist for Critical Appraisal of Economical Evaluation)*[40]

Item no.[a]	Bergman et al[57–60]	Bosmans et al[45–47]	Critchley et al[69]	Korthals-de Bos et al[63,64]	Lewis et al[65,66]	Lin et al[67,68]	Niemisto et al[53,54]	Rivero-Arias et al[55,56]	UK BEAM[50–52]	Whitehurst et al[61,62]	Williams et al[48,49]
Item 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 4	Yes	Yes	Can't tell (costs)	Yes	No (costs)	Yes	Yes	Yes	Yes	Yes	Yes
Item 5	Can't tell (costs)	Yes	Can't tell (costs)	Can't tell (costs)	Can't tell (costs)	Can't tell (costs)	Can't tell (costs)	Yes	Yes	Yes	Yes
Item 6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 8	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Item 9	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Item 10	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	% of items with "yes" on Drummond checklist										
	90	100	80	80	80	70	90	100	100	100	100

Item 1: Was a well-defined question posed in answerable form? Item 2: Was a comprehensive description of the competing alternatives given? Item 3: Was the effectiveness of the programmes or services established? Item 4: Were all the important and relevant costs and consequences for each alternative identified? Item 5: Were costs and consequences measured accurately in appropriate physical units (e.g. number of physician visits, lost work-days, gained life-years)? Item 6: Were costs and consequences valued credibly? Item 7: Were costs and consequences adjusted for differential timing? Item 8: Was an incremental analysis of costs and consequences of alternatives performed? Item 9: Was allowance made for uncertainty in the estimates of costs and consequences? Item 10: Did the presentation and discussion of study results include all issues of concern to users?

[a] Responses to items: yes, no, can't tell.

The trial by Niemisto et al[53,54] evaluated the cost-effectiveness of combination of manual therapy, stabilization exercise, and physician consultation compared with physician consultation alone in patients with low back pain. This study demonstrated significantly reduced pain intensity for the combination treatment compared with physician consultation alone at 24-month follow-up (visual analog scale [VAS] score: 30.7 vs 33.1, $P = .01$). The associated ICER was £165 per score improvement on VAS and was £384 per score improvement on disability scale.

The trial by Rivero-Arias et al[55,56] compared physiotherapy with physiotherapist advice in participants with low back pain. At 12 months of follow-up, physiotherapy was more expensive (£320 vs £247) and more effective (QALYs gained: 0.74 vs 0.69) than the physiotherapist advice group, but neither the incremental mean costs nor the incremental mean QALYs between the 2 treatment groups was statistically significant. The cost per QALY gained was £1454. If the decision maker is willing to pay £5000, the probability of physiotherapy being more cost-effective than physiotherapist advice was 60%.

The UK BEAM[50–52] assessed the cost-utility of adding manipulation, or exercise, or manipulation followed by exercise to GP care in patients with low back pain. For 12 months, all 3 groups of exercise (£631), manipulation (£702), and manipulation plus exercise (£612) incurred higher mean total costs compared with GP care (£449). The mean number of QALYs gained was also greater for the 3 groups (0.635, 0.659, and 0.651, respectively) compared with GP care (0.618). The ICERs for adding manipulation alone, exercise alone, or manipulation plus exercise to GP care relative to GP care alone were £6175, £10 692, and £4918, respectively. The combination of manipulation and exercise dominated exercise alone because of lower costs and better outcomes in terms of the number of QALYs gained. The findings of this study also indicated that for additional £91, manipulation alone could gain an extra 0.008 QALYs compared with manipulation plus exercise (ICER of £11 360). If the decision maker was willing to pay £10 000, the most cost-effective treatment option for patients with low back pain was the addition of manipulation to GP care.

Whitehurst et al[61,62] compared manual physiotherapy with a brief pain management program in patients with acute low back pain. At 12 months of follow-up, the mean cost per patient for the manual physiotherapy was greater compared with brief pain management, with a mean difference of £66. Although the gains in disability (Roland-Morris Disability Questionnaire [RMDQ] mean score, 0.33) and utility (mean QALYs, 0.022) were in favor of manual physiotherapy vs brief pain management, these differences were not statistically significant. The ICER for manual physiotherapy relative to brief pain management was £3006 per QALY gained. If the NHS were willing to pay £10 000 per QALY gained, there was 83% chance that manual physiotherapy was more cost-effective compared with brief pain management.

Neck Pain. In 1 trial,[45–47] Bosmans et al evaluated the cost-effectiveness of behavioral graded activity program relative to manual therapy in patients with neck pain. Compared with manual therapy, treatment with behavioral graded activity was associated with a statistically significant reduction in pain intensity (mean VAS score, 0.88) and disability (mean Neck Disability Index score, 2.40). Behavioral graded activity was shown to be more cost-

Table 3. *Risk of Bias Assessment of the Included RCTs (Adapted From van Tulder et al[41])*

ROB Item	Bergman et al[57–60]	Bosmans et al[45–47]	Critchley et al[69]	Korthals-de Bos et al[63,64]	Lewis et al[65,66]	Lin et al[67,68]	Niemisto et al[53,54]	Rivero-Arias et al[55,56]	UK BEAM[50–52]	Whitehurst et al[61,62]	Williams et al[48,49]
Was the method of randomization adequate?	Don't know	Yes	Yes	Yes	Yes	Yes	Don't know	Yes	Yes	Yes	Yes
Was the treatment allocation concealed?	Yes	Yes	Yes	Yes	Don't know	Yes	Yes	Yes	Yes	Yes	Don't know
Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes
Was the patient blinded to the intervention?	No	No	No	No	No	No	No	No	No	No	No
Was the care provider blinded to the intervention?	Don't know	Don't know	No	No	No	No	No	No	No	No	Don't know
Was the outcome assessor blinded to the intervention?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were cointerventions avoided or similar?	Don't know	Don't know	Yes	No	No	Don't know	Yes	No	Don't know	No	Don't know
Was the compliance acceptable in all groups?	Yes	No	Don't know	No	Yes	Yes	Yes	Yes	Don't know	No	Don't know
Was the dropout rate described and acceptable?	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Was the timing of the outcome assessment in all groups similar?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Summary ROB	Low ROB	Low ROB	Low ROB	High ROB	High ROB	Low ROB	Low ROB	High ROB	Low ROB	Low ROB	High ROB

Yes, if item is satisfied; no, if item is not satisfied; Don't know, unclear if item was satisfied or not; Low ROB, if 6 or more items are satisfied (rated as "yes"); High ROB, if 5 or fewer items are satisfied (rated as "yes").
NA, not applicable; *ROB*, risk of bias.

effective than manual therapy in reducing pain intensity (ICER: £388 per improvement in pain score) and disability (ICER: £152 per improvement in disability score) but not for perceived recovery (ICER: £17 444 per improvement in recovery score).

One trial by Korthals-de Bos et al[63,64] evaluated manual therapy, physiotherapy, and GP care in patients with neck pain. After 1 year of follow-up, manual therapy was significantly less costly than physiotherapy (−£1149) and GP care (−£1260). Moreover, manual therapy was significantly more effective in reducing neck pain than physiotherapy (mean difference, 1.20), but not disability (mean difference, 0.90). The mean differences in pain intensity (0.10) and disability (−1.40) between manual therapy and GP care were not statistically significant. The manual therapy demonstrated dominance (both less costly and more effective) over both physiotherapy and GP care for perceived recovery and utility. Also, manual therapy was dominant over physiotherapy for pain intensity. Physiotherapy and GP care did not differ in either costs or in improving neck pain or disability.

Lewis et al[65,66] conducted an economic evaluation in which A&E plus manual therapy or pulsed shortwave diathermy was compared with A&E alone in patients with neck pain. At 6 months, the differences in costs, disability, and QALYs gained between the treatment groups were not statistically significant. In terms of societal perspective, for disability, the A&E plus manual therapy had a higher probability of being cost-effective (up to 55%) than A&E

Table 4. *Cost-Effectiveness/Cost-Utility of Manual Therapy Interventions According to Condition – RCTs*

Study ID	Analysis	Health Outcomes	Mean Costs Mean (SD) Health Effects	Difference in Costs Incremental Ratio
Spinal (upper/low back, neck, or both) pain				
Williams 2004 [48,49] UK [a]	**Analysis:** CUA **Statistical analysis:** Non-parametric bootstrap (1000 simulations)	EuroQoL EQ-5D	**OSM + Usual GP care** **Costs:** £402 **Health effects** EQ-5D: 0.717 (0.248) QALY: 0.056 (0.101) **Usual GP care** **Costs:** £286 **Health effects** EQ-5D: 0.656 (0.289) QALY: 0.031 (0.105)	**Incremental Costs:** £117 **Cost per QALY gained:** £4674
Low Back Pain				
Critchley 2007 [69] UK [b]	**Analysis:** CUA **Statistical analysis:** ANOVA, non-parametric bootstrap (number of simulations: NR)	EuroQoL EQ-5D	**Individual PT** **Costs:** £574 **Health effects** EQ-5D: 0.67 QALY: 0.990 **Spinal stabilisation PT** **Costs:** £459 **Health effects** EQ-5D: 0.63 QALY: 0.900 **Pain management** **Costs:** £200 **Health effects** EQ-5D: 0.68 QALY: 1.000	**Individual PT – spinal stabilisation** **Incremental Costs:** £115 **Cost per QALY gained:** £1279 **Cost per QALY gained:** Pain management dominant over both treatments (individual PT and spinal stabilisation)
Niemisto 2005 [53,54] Finland [b]	**Analysis:** CEA **Statistical analysis:** Repeated measures ANOVA, Intention to Treat analysis, bootstrap technique (5000 simulations)	Pain (visual analogue score), Oswestry Disability Index (ODI), 15-D (HRQoL)	**MT + exercise + GP advice** **Costs:** £4568 **Health effects:** NR **GP advice** **Costs:** £5643 **Health effects:** NR	**Incremental Costs:** -£1075 **Cost per unit of outcome improved in:** Pain (VAS) £165 Disability (ODI) £384
Rivero-Arias 2006 [55,56] UK [a]	**Analysis:** CUA **Statistical analysis:** Mean differences and 95% CI using independent sample t test (for costs) and ANCOVA (for QALYs), multiple imputation for missing values using linear regression technique	EuroQoL EQ-5D	**PT** **Costs:** £320 **Health effects** EQ-5D: 0.73 (0.25) QALY: 0.740 (0.18) **Physiotherapist advice** **Costs:** £247 **Health effects** EQ-5D: 0.72 (0.26) QALY: 0.690 (0.23)	**Incremental Costs:** £73 **Cost per QALY gained:** £1454
UK BEAM 2004 [50–52] UK [b]	**Analysis:** CUA **Statistical analysis:** Bayesian Markov Chain Monte Carlo multilevel analysis	EuroQoL EQ-5D	**GP (Best) care + manipulation** **Costs:** £702 **Health effects** QALY 0.659 **GP (Best) care + manipulation + exercise** **Costs:** £612 **Health effects** QALY: 0.651 **GP (Best) care + exercise** **Costs:** £631	**GP (Best) care + manipulation - GP (Best) care** **Incremental costs:** £253 **Cost per QALY gained:** £6175 **GP (Best) care + manipulation + exercise - GP (Best) care** **Incremental costs:** £162

(continued on next page)

Table 4. (*continued*)

Study ID	Analysis	Health Outcomes	Mean Costs Mean (SD) Health Effects	Difference in Costs Incremental Ratio
			Health effects QALY: 0.635 **GP (Best) care** **Costs:** £449 **Health effects** QALY: 0.618	**Cost per QALY gained:** £4918 Dominant over GP (Best) care + exercise **GP (Best) care + exercise - GP (Best) care** **Incremental costs:** £182 **Cost per QALY gained:** £10692
Whitehurst 2007 [61,62] UK [b]	**Analysis:** CUA, CEA **Statistical analysis:** Intention to Treat analysis, multiple imputation based on multiple linear regression models, 95% CIs based on parametric tests if normal distribution, and if skewed, bootstrapping technique (5000 simulations)	Disability (RMDQ score), EuroQoL EQ-5D	**Manual PT** **Costs:** £246 **Health effects** Mean change disability (RMDQ): 8.887 QALY: 0.777 **BPM** **Costs:** £180 **Health effects** Mean change disability (RMDQ): 8.553 QALY: 0.755	**Incremental costs:** -£66 **Cost per RMDQ change:** £198 **Cost per QALY gained:** £3006
Neck Pain				
Bosmans 2011 [45–47] Netherlands [b]	**Analysis:** CEA **Statistical analysis:** Intention to Treat analysis, multiple imputation, CIs based on bootstrapping (5000 simulations)	Pain (VAS), disability (NDI), perceived recovery, and quality of life (SF-12)	**SMT (MOB + MAN)** **Costs:** £823 **Health effects** Mean change VAS: -3.5 (SE 0.31) NDI: -8.3 (SE 0.77) Recovery: 0.76 (SE 0.05) QALY: 0.770 (SE 0.01) **BGA (increasing exercise program)** **Costs:** £1,174 **Health effects** Mean change VAS: - 4.4 (SE 0.31) NDI: -10.6 (SE 0.79) Recovery: 0.78 (SE 0.05) QALY: 0.750 (SE 0.01)	**Incremental costs:** -£349 **Cost per unit of outcome improved in:** BGA versus SMT Recovery: £17,444 Pain: £388 NDI: £152 **Cost per QALY gained:** £17444
Korthals-de Bos 2003 [63,64] Netherlands [a]	**Analysis:** CUA, CEA **Statistical analysis:** Intention to Treat analysis, CIs based on bootstrapping (500 simulations), ICERs based on bootstrapping (5000 simulations)	Pain (VAS), disability (NDI), perceived recovery, EuroQoL EQ-5D	**SMT (mobilisation)** **Costs:** £604 **Health effects** Mean change VAS: 4.2 (2.4) NDI: 7.2 (7.5) Recovery: 71.7 (43) Utility: 0.820 (0.13) **PT** **Costs:** £1753 **Health effects** Mean change VAS: 3.1 (2.9) NDI: 6.3 (8.0) Recovery: 62.7 (37) Utility: 0.790 (0.14) **GP care** **Costs:** £1864 **Health effects**	**SMT (mobilisation) – GP care** **Incremental costs:** -£1260 **PT – GP care** **Incremental costs:** -£111 **Cost per unit of outcome improved in:** Dominance of SMT over GP care and PT in terms of recovery and pain **Cost per QALY gained:** Dominance of SMT over GP care and PT in terms of QALYs **Cost per unit of outcome improved in:** PT over GP care

Table 4. (*continued*)

Study ID	Analysis	Health Outcomes	Mean Costs Mean (SD) Health Effects	Difference in Costs Incremental Ratio
			Mean change VAS: 4.1 (2.9) NDI: 8.5 (7.4) Recovery: 56.3 (36) Utility: 0.770 (0.16)	Pain £111 NDI £50 **Cost per QALY gained:** Dominance of PT over GP care in terms of QALYs
Lewis 2007 [65,66] UK [a]	**Analysis:** CUA, CEA **Statistical analysis:** Intention to Treat analysis, CIs for differences in means using parametric methods, CIs for uncertainty in cost estimates were based on bootstrapping (5000 simulations), linear regression to adjust for baseline covariates, multiple imputation technique to account for missing data	Disability (NPQ), EuroQoL EQ-5D	**SMT (MOB + MAN) + A&E** **Costs:** £367 **Health effects** NPQ: 10.2 (14.1) QALY: 0.342 (0.114) **PSWD + A&E (advice + exercise)** **Costs:** £410 **Health effects** NPQ: 10.3 (15.0) QALY: 0.360 (0.094) **A&E (advice + exercise)** **Costs:** £452 **Health effects** NPQ: 11.5 (15.7) QALY: 0.362 (0.114)	**SMT (MOB + MAN) + A&E - A&E (advice + exercise)** **Incremental costs:** -£84 **PSWD + A&E (advice + exercise) - A&E (advice + exercise)** **Incremental costs:** -£42 **Cost per unit of outcome improved in NPQ:** A&E over SMT £65 **Cost per QALY gained:** A&E over SMT £4672
Shoulder Pain				
Bergman 2010 [57–60] Netherlands [b]	**Analysis:** CEA **Statistical analysis:** paired sample t-test, bootstrapping (2000 replications) to compare mean costs between the groups and estimate 95% CIs, Intention to Treat analysis	Perceived recovery (%), shoulder pain, shoulder disability, general health	**SMT (MOB + MAN) + GP care** **Costs:** £1443 **Health effects** Recovery: 41% Pain: 5.9 (5.4) Disability: 33.0 (34.6) General health: 0.11 (0.19) **GP care** **Costs:** £686 **Health effects** Recovery: 35% Pain: 5.2 (5.5) Disability: 20.3 (35.9) General health: 0.08 (0.21)	**Incremental costs:** £757 **Cost per unit of outcome improved in:** Recovery: £151 Pain: £1081 Disability: £60 General health: £25222
Ankle Fracture				
Lin 2008 [67,68] Australia [b]	**Analysis:** CUA **Statistical analysis:** Intention to Treat analysis, ANCOVA for group-differences, imputation of missing values, two sample t-test and bootstrapping (1000 replications) 95% CIs for group-differences in costs	Quality of life (AQoL), activity limitation (LEFS)	**MT + PT** **Costs:** £2267 **Health effects:** NR **PT** **Costs:** £1754 **Health effects:** NR	**Incremental costs:** £513 **Incremental effects:** between-group difference AQoL: 1.3 (0.1, 2.5) QALY: -0.09 (-0.6, 0.4) **Cost per QALY gained:** -£1075

AQoL, assessment of quality of life; *BGA*, behavioral graded activity; *BPM*, brief pain management; *CEA*, cost-effectiveness analysis; *CI*, confidence interval; *CUA*, cost-utility analysis; *EQ-5D*, European Quality of Life-5 Dimensions; *GP*, general practitioner; *HRQoL*, health-related quality of life; *LEFS*, lower extremity functional scale; *MAN*, manipulation; *MOB*, mobilization; *MT*, manual therapy; *NDI*, Neck Disability Score; *NPQ*, Northwick Park Neck Pain Questionnaire; *NR*, not reported; *ODI*, Oswestry Disability Index; *OSM*, osteopathic manual therapy; *PT*, physiotherapy; *QALY*, quality-adjusted life year; *RMDQ*, Roland-Morris Disability; *SMT*, spinal manual therapy; *VAS*, visual analogue scale.

[a] High risk of bias (≤ 5 items of the recommended criteria by the Cochrane

[b] Low risk of bias (≥ 6 items of the recommended criteria by the Cochrane Back Review Group were satisfied)

alone or A&E plus pulsed shortwave diathermy (PSWD), but only at WTP thresholds of less than £100. For QALYs, at £30 000 per QALY gained threshold, the probabilities for A&E alone, A&E plus manual therapy, and A&E plus PSWD were 30%, 44%, and 26%, respectively.

Shoulder Pain. The trial by Bergman et al[57–60] evaluated spinal manual therapy plus usual GP care (relative to usual GP care alone in patients with shoulder pain. At 6 months of follow-up, the manual therapy group incurred nonsignificantly higher total costs compared with the GP care alone group (mean difference, £757). The mean improvements in perceived recovery (5.0%), shoulder pain (0.7), and general health (0.03) were in favor of the manual therapy group, but the differences were not statistically significant. The mean shoulder disability score was the only outcome significantly favoring the manual therapy over GP care (12.7). The ICERs for the manual therapy plus GP care vs GP care alone for perceived recovery, pain, disability, and general health were £151, £1081, £60, and £25 222, respectively.

Ankle Fracture. Lin et al[67,68] compared manual therapy added to physiotherapy with physiotherapy in patients with ankle fractures. At 6 months of follow-up, the mean between-group differences in mean AQoL score (1.3, $P = .04$), lower extremity function (−1.0, $P = .70$), and QALYs gained (−0.09) were not statistically significant. Similarly, there was no difference in total health care costs between the study groups (£513).

Discussion

This review identified limited evidence indicating that manual therapy techniques (eg, osteopathic spinal manipulation, physiotherapy consisting of manipulation and mobilization techniques, and chiropractic manipulation), in addition to other treatments or alone, are more cost-effective than usual GP care (alone or with exercise), spinal stabilization, GP advice, advice to remain active, or brief pain management for improving low back pain and/or disability. Similarly, one study[57] demonstrated that spinal manipulation in addition to GP care was more cost-effective than GP care alone in reducing shoulder pain and related disability. The extra costs needed for 1-unit improvement in low back or shoulder pain/disability score or 1 QALY gained were lower than the WTP thresholds reported across the studies.

The cost-effectiveness of manual therapy for improving neck pain, disability, and QALYs gained in comparison with other treatments was not consistent across the studies. For example, one trial[63,64] demonstrated the domination of chiropractic manipulation over physiotherapy or GP care in improving neck pain and QALYs gained. In 2 other trials, either alternative intervention (behavioral graded activity) was more cost-effective than manual therapy[45] or the probability for manual therapy being more cost-effective compared with advice plus exercise was too low.[65]

The evidence regarding cost-effectiveness of manual therapy compared with physiotherapy for reducing pain and disability related to ankle fractures, as reported in one study,[67] has been insufficient and inconclusive because of small sample size and uncertainty around the cost-effectiveness measure.

It is difficult to draw definitive conclusions regarding the comparative cost-effectiveness of manual therapy techniques in patients with spinal pain due to the paucity, clinical heterogeneity (eg, different techniques, wide variety of comparators), and study-related shortcomings (eg, small sample, short follow-up, high uncertainty in the estimates of ICERs) of the identified evidence. For example, the use of different manual therapy techniques (eg, manipulation, mobilization, and chiropractic care) in combination with other interventions (eg, physiotherapy, exercise, and GP care) leads to differential effectiveness profiles, thereby limiting the comparability of results across studies. The nonspecific or contextual effects (eg, intervention fidelity, placebo effect, practitioner's experience) due to the complexity of interventions and lack of patient blinding may have biased the study results for subjective outcome measures such as pain, disability, and QOL. Because none of the studies used a sham/control arm, it is difficult to tease out the specific effects of treatment from patients' differential expectation (or practitioner's experience/skill set) across the study treatment arms.[70]

All the included studies were trial-based economic evaluations. None of the studies used economic modeling to extrapolate beyond the trial data to look at the longer-term cost-effectiveness of the different interventions. Studies reporting cost-effectiveness acceptability curves (CEACs) used bootstrapping, none of the studies used simple one-way or multiway sensitivity analyses to check for uncertainty in any of the key cost factors, which may be driving the ICER.

Limitations and Strengths

The findings of this review are not directly comparable with those of other systematic reviews,[28–33,71–81] given the differences in scope, research question, study inclusion/exclusion criteria, types of economic evaluation, and interventions. The findings of these reviews were either inconclusive because of the paucity and heterogeneity of the evidence for manual therapy[28–33] or showed some cost-effectiveness of manual therapy over alternative treatments (eg, usual care and exercise).[71,75,76,78,79,81]

The applicability of findings of the included studies, despite them being pragmatic, may be limited to only countries with similar health care system and considerations of utility (eg, calculations based on the same QOL instrument). The applicability may also be limited by the

differences in components of manual therapy interventions and short follow-ups of the studies.

The strengths of the current review include the reviewer's use of systematic and independent strategies to minimize the ROB in searching, identifying, selecting, extracting, and appraising the primary studies. The search strategy was applied to multiple electronic databases and other sources such as references of relevant primary studies and systematic reviews. Also, this review summarized the evidence from studies that evaluated costs and effectiveness simultaneously through cost-effectiveness and/or CUAs by providing ICERs. As a limitation, this review included only RCT-based cost-effectiveness evaluations.

This paper provides a platform for further research into the cost-effectiveness of manual therapy for the management of musculoskeletal conditions. The findings underscore the paucity of good-quality published evidence on this issue. This is based on the small number of identified RCTs focus of which is rather limited (ie, nonspecific spinal pain). The insufficient evidence on cost-effectiveness may be explained by difficulties in obtaining cost data, lack of expertise in economic outcomes, and/or perceived societal discomfort with assigning monetary units to human health.[32] Raising awareness among the chiropractic community about the importance of undertaking more high quality economic evaluations is needed.

Because several studies did not use QALYs as an outcome measure, this presents difficulty for decision makers if they wish to compare value for money across musculoskeletal conditions with other health conditions such as cancer and cardiovascular disease, in line with the cost-effectiveness thresholds set by NICE. Consideration of the competing demand/supply side issues of manual therapy and how these issues may vary across countries is needed. Furthermore, it is not clear whether the affordability of manual therapy in countries where the provision of such services fall outside publicly funded arrangements is likely to influence utilization; this raises questions about the generalizability of the current reported findings.

We recommend that future studies report unit cost calculation with costs broken down by each service to allow the judgment as to whether all relevant costs for a given perspective were considered and how the total costs were calculated. If ethically justifiable, future trials need to include sham or no treatment arm to allow the assessment and separation of nonspecific effects (eg, patient's expectation) from treatment effects. More exploration is warranted about which characteristics of manual therapy (eg, mode/frequency of administration or choice of spinal regions) are important for clinically relevant and patient-centered outcomes. Finally, greater consideration is needed to improve reporting quality of primary studies evaluating manual therapy.

Conclusions

Preliminary evidence from this review shows some economic advantage of manual therapy relative to other interventions used for the management of musculoskeletal conditions. However, at present, there is a paucity of evidence on the cost-effectiveness and/or cost-utility evaluations for manual therapy interventions. Further improvements in the methodological conduct and reporting quality of economic evaluations of manual therapy are warranted in order to facilitate adequate evidence-based decisions among policy makers, health care practitioners, and patients.

Practical Applications

- There is some limited evidence indicating that manual therapy techniques are more cost-effective than usual GP care, spinal stabilization, GP advice, advice to remain active, or brief pain management for improving low back and shoulder pain/disability.
- The extra costs needed for 1-unit improvement in low back or shoulder pain/disability score or 1 QALY gained were lower than the WTP thresholds reported across the studies.
- The cost-effectiveness of manual therapy for improving neck pain, disability, and QALYs gained in comparison with other treatments was not consistent across the studies.

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Contributorship Information

Concept development (provided idea for the research): P.S.
Design (planned the methods to generate the results): A.T., C.C., R.C., P.S.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): P.S., A.C.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): C.C.

Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): A.T., C.C., H.M.

Literature search (performed the literature search): A.T., C.C., R.C.

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Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): A.T., C.C., H.M., P.S.

References

1. Farrell JP, Jensen GM. Manual therapy: a critical assessment of role in the profession of physical therapy. Phys Ther 1992; 72:843-52.
2. DeStefano LA, Greenman PE. Greenman's principles of manual medicine. 4th ed. Lippincott Williams & Wilkins; 2010.
3. Jette AM, Delitto A. Physical therapy treatment choices for musculoskeletal impairments. Phys Ther 1997;77:145-54.
4. Bryans R, Decina P, Descarreaux M, et al. Evidence-based guidelines for the chiropractic treatment of adults with neck pain. J Manipulative Physiol Ther 2014;37:42-63.
5. Brantingham JW, Cassa TK, Bonnefin D, et al. Manipulative and multimodal therapy for upper extremity and temporomandibular disorders: a systematic review. J Manipulative Physiol Ther 2013;36:143-201.
6. Bryans R, Descarreaux M, Duranleau M, et al. Evidence-based guidelines for the chiropractic treatment of adults with headache. J Manipulative Physiol Ther 2011;34:274-89.
7. Farabaugh RJ, Dehen MD, Hawk C. Management of chronic spine-related conditions: consensus recommendations of a multidisciplinary panel. J Manipulative Physiol Ther 2010;33:484-92.
8. Lawrence DJ, Meeker W, Branson R, et al. Chiropractic management of low back pain and low back-related leg complaints: a literature synthesis. [Review] [126 refs] 2008; 31:659-74.
9. Globe GA, Morris CE, Whalen WM, Farabaugh RJ, Hawk C. Chiropractic management of low back disorders: report from a consensus process. J Manipulative Physiol Ther 2008;31:651-8.
10. Furlan AD, Yazdi F, Tsertsvadze A, et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. Evid Based Complement Alternat Med 2012; 2012:953139. http://dx.doi.org/10.1155/2012/953139. [Epub 2011 Nov 24].
11. Shekelle PG. The appropriateness of spinal manipulation for low-back pain: project overview and literature review. 1st ed. Rand Corp; 1991.
12. Shekelle PG, Adams AH, Chassin MR, Hurwitz EL, Brook RH. Spinal manipulation for low-back pain. Ann Intern Med 1992;117:590-8.
13. Bigos SJ, United States, Agency for Health Care Policy and Research, American HC. Acute low back problems in adults. US Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1994.
14. Di Fabio RP. Clinical assessment of manipulation and mobilization of the lumbar spine. A critical review of the literature. Phys Ther 1986;66:51-4.
15. Ottenbacher K, DiFabio RP. Efficacy of spinal manipulation/mobilization therapy. A meta-analysis. Spine (Phila Pa 1976) 1985;10:833-7.
16. Bronfort G, Assendelft WJ, Evans R, Haas M, Bouter L. Efficacy of spinal manipulation for chronic headache: a systematic review. J Manipulative Physiol Ther 2001;24:457-66.
17. Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. Chiropr Osteopat 2010;18:3.
18. Assendelft WJ, Morton SC, Yu EI, Suttorp MJ, Shekelle PG. Spinal manipulative therapy for low back pain. A meta-analysis of effectiveness relative to other therapies. Ann Intern Med 2003;138:871-81.
19. Cherkin DC, Deyo RA, Battie M, Street J, Barlow W. A comparison of physical therapy, chiropractic manipulation, and provision of an educational booklet for the treatment of patients with low back pain. N Engl J Med 1998;339:1021-9.
20. Ernst E. Adverse effects of spinal manipulation: a systematic review. J R Soc Med 2007;100:330-8.
21. Ernst E. Deaths after chiropractic: a review of published cases. Int J Clin Pract 2010;64:1162-5.
22. Carnes D, Mars TS, Mullinger B, Froud R, Underwood M. Adverse events and manual therapy: a systematic review. Man Ther 2010;15:355-63.
23. Gouveia LO, Castanho P, Ferreira JJ. Safety of chiropractic interventions: a systematic review. Spine (Phila Pa 1976) 2009;34:E405-13.
24. Rubinstein SM, Peerdeman SM, van Tulder MW, Riphagen I, Haldeman S. A systematic review of the risk factors for cervical artery dissection. Stroke 2005;36:1575-80.
25. Vohra S, Johnston BC, Cramer K, Humphreys K. Adverse events associated with pediatric spinal manipulation: a systematic review. Pediatrics 2007;119:e275-83.
26. Stevinson C, Ernst E. Risks associated with spinal manipulation. Am J Med 2002;112:566-71.
27. Carlesso LC, Gross AR, Santaguida PL, Burnie S, Voth S, Sadi J. Adverse events associated with the use of cervical manipulation and mobilization for the treatment of neck pain in adults: a systematic review. Man Ther 2010; 15:434-44.
28. Maund E, Craig D, Suekarran S, et al. Management of frozen shoulder: a systematic review and cost-effectiveness analysis. Health Technol Assess 2012;16:1-264.
29. Indrakanti SS, Weber MH, Takemoto SK, Hu SS, Polly D, Berven SH. Value-based care in the management of spinal disorders: a systematic review of cost-utility analysis. Clin Orthop Relat Res 2012;470:1106-23.
30. Driessen MT, Lin CW, van Tulder MW. Cost-effectiveness of conservative treatments for neck pain: a systematic review on economic evaluations. Eur Spine J 2012;21:1441-50.
31. Furlan AD, Yazdi F, Tsertsvadze A, et al. Complementary and alternative therapies for back pain II. Evidence Report/Technology Assessment No. 194. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. 290-2007-10059-I (EPCIII). AHRQ Publication No.(11) E007. Rockville, MD: Agency for Healthcare Research and Quality; October 2010.
32. Dagenais S, Roffey DM, Wai EK, Haldeman S, Caro J. Can cost utility evaluations inform decision making about interventions for low back pain? [Review] [69 refs]Spine J 2009;9:944-57.
33. Brown A, Angus D, Chen S, et al. Costs and outcomes of chiropractic treatment for low back pain [Technology report no 56]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005.
34. Stevans JM, Zodet MW. Clinical, demographic, and geographic determinants of variation in chiropractic episodes of care for adults using the 2005-2008 Medical Expenditure Panel Survey. J Manipulative Physiol Ther 2012;35:589-99.

35. Grieves B, Menke JM, Pursel KJ. Cost minimization analysis of low back pain claims data for chiropractic vs medicine in a managed care organization. [Erratum appears in J Manipulative Physiol Ther. 2010 Feb;33(2):164]. J Manipulative Physiol Ther 2009;32:734-9.
36. Haas M, Sharma R, Stano M. Cost-effectiveness of medical and chiropractic care for acute and chronic low back pain. J Manipulative Physiol Ther 2005;28:555-63.
37. Glanville J, Kaunelis D, Mensinkai S. How well do search filters perform in identifying economic evaluations in MEDLINE and EMBASE. Int J Technol Assess Health Care 2009;25:522-9.
38. World Bank. World Economic Outlook Database. WorldBank, International Monetary Fund; 2014 [Accessed March 26, 2014 http://www.imf.org/external/pubs/ft/weo/2004/01/data/].
39. Organisation for Economic Co-operation and Development. Annual national accounts: PPPs and exchange rates. National Accounts Statistics (database); 2014 [Accessed March 26, 2014 http://www.oecd.org/std/prices-ppp/purchasingpowerparitiespppsdata.htm].
40. Drummond MF, Sculpher MJ, Torrance GW. Methods for the economic evaluation of health care programmes. 3rd ed. USA: Oxford University Press; 2005.
41. van Tulder MW, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. Spine (Phila Pa 1976) 2003;28:1290-9.
42. van Tulder MW, Suttorp M, Morton S, Bouter LM, Shekelle P. Empirical evidence of an association between internal validity and effect size in randomized controlled trials of low-back pain. Spine (Phila Pa 1976) 2009;34:1685-92.
43. Balk EM, Bonis PA, Moskowitz H, et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. JAMA 2002;287:2973-82.
44. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609-13.
45. Bosmans JE, Pool JJM, de Vet HCW, van Tulder MW, Ostelo RWJG. Is behavioral graded activity cost-effective in comparison with manual therapy for patients with subacute neck pain? An economic evaluation alongside a randomized clinical trial. Spine 2011;36:E1179-86.
46. Pool JJ, Ostelo RW, Koke AJ, Bouter LM, de Vet HC. Comparison of the effectiveness of a behavioural graded activity program and manual therapy in patients with subacute neck pain: design of a randomized clinical trial. Man Ther 2006;11:297-305.
47. Pool JJ, Ostelo RW, Knol DL, Vlaeyen JW, Bouter LM, de Vet HC. Is a behavioral graded activity program more effective than manual therapy in patients with subacute neck pain? Results of a randomized clinical trial. Spine 2010;35:1017-24.
48. Williams NH, Edwards RT, Linck P, et al. Cost-utility analysis of osteopathy in primary care: results from a pragmatic randomized controlled trial. Fam Pract 2004;21:643-50.
49. Williams NH, Wilkinson C, Russell I, et al. Randomized Osteopathic Manipulation Study (ROMANS): pragmatic trial for spinal pain in primary care. Fam Pract 2003;20:662-9.
50. UK BEAM Trial Team. United Kingdom Back Pain Exercise and Manipulation (UK BEAM) randomised trial: cost effectiveness of physical treatments for back pain in primary care. BMJ 2004;329:1381.
51. Brealey S, Burton K, Coulton S, et al. UK Back pain Exercise and Manipulation (UK BEAM) trial—national randomised trial of physical treatments for back pain in primary care: objectives, design and interventions [ISRCTN32683578]. BMC Health Serv Res 2003;3:16.
52. UK BEAM Trial Team. United Kingdom Back Pain Exercise and Manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ 2004;329:1377.
53. Niemisto L, Rissanen P, Sarna S, Lahtinen-Suopanki T, Lindgren KA, Hurri H. Cost-effectiveness of combined manipulation, stabilizing exercises, and physician consultation compared to physician consultation alone for chronic low back pain: a prospective randomized trial with 2-year follow-up. Spine 2005;30:1109-15.
54. Niemisto L, Lahtinen-Suopanki T, Rissanen P, Lindgren KA, Sarna S, Hurri H. A randomized trial of combined manipulation, stabilizing exercises, and physician consultation compared to physician consultation alone for chronic low back pain. Spine 2003;28:2185-91.
55. Rivero-Arias O, Gray A, Frost H, Lamb SE, Stewart-Brown S. Cost-utility analysis of physiotherapy treatment compared with physiotherapy advice in low back pain. Spine (Phila Pa 1976) 2006;31:1381-7.
56. Frost H, Lamb SE, Doll HA, Carver PT, Stewart-Brown S. Randomised controlled trial of physiotherapy compared with advice for low back pain. BMJ 2004;329:708.
57. Bergman GJ, Winter JC, van Tulder MW, Meyboom-de JB, Postema K, van der Heijden GJ. Manipulative therapy in addition to usual medical care accelerates recovery of shoulder complaints at higher costs: economic outcomes of a randomized trial. BMC Musculoskelet Disord 2010;11:200.
58. Bergman GJD, Winters JC, van der Heijden GJMG, Postema K, Meyboom-de Jong B. Groningen Manipulation Study. The effect of manipulation of the structures of the shoulder girdle as additional treatment for symptom relief and for prevention of chronicity or recurrence of shoulder symptoms. Design of a randomized controlled trial within a comprehensive prognostic cohort study. J Manipulative Physiol Ther 2002;25:543-9.
59. Bergman GJD, Winters JC, Groenier KH, et al. Manipulative therapy in addition to usual medical care for patients with shoulder dysfunction and pain: a randomized, controlled trial. Ann Intern Med 2004;141:432-9.
60. Bergman GJ, Winters JC, Groenier KH, Meyboom-de JB, Postema K, van der Heijden GJ. Manipulative therapy in addition to usual care for patients with shoulder complaints: results of physical examination outcomes in a randomized controlled trial. J Manipulative Physiol Ther 2010;33:96-101.
61. Whitehurst DG, Lewis M, Yao GL, et al. A brief pain management program compared with physical therapy for low back pain: results from an economic analysis alongside a randomized clinical trial. Arthritis Rheum 2007;57:466-73.
62. Hay EM, Mullis R, Lewis M, et al. Comparison of physical treatments versus a brief pain-management programme for back pain in primary care: a randomised clinical trial in physiotherapy practice. Lancet 2005;365:2024-30.
63. Korthals-de Bos IBC, Hoving JL, van Tulder MW, et al. Cost effectiveness of physiotherapy, manual therapy, and general practitioner care for neck pain: economic evaluation alongside a randomised controlled trial. BMJ 2003;326:911.
64. Hoving JL, Koes BW, de Vet HC, et al. Manual therapy, physical therapy, or continued care by a general practitioner for patients with neck pain. A randomized, controlled trial. Ann Intern Med 2002;136:713-22.
65. Lewis M, James M, Stokes E, et al. An economic evaluation of three physiotherapy treatments for non-specific neck

disorders alongside a randomized trial. Rheumatology (UK) 2007;46:1701-8.
66. Dziedzic K, Hill J, Lewis M, Sim J, Daniels J, Hay EM. Effectiveness of manual therapy or pulsed shortwave diathermy in addition to advice and exercise for neck disorders: a pragmatic randomized controlled trial in physical therapy clinics. Arthritis Rheum 2005;53:214-22.
67. Lin CW, Moseley AM, Haas M, Refshauge KM, Herbert RD. Manual therapy in addition to physiotherapy does not improve clinical or economic outcomes after ankle fracture. J Rehabil Med 2008;40:433-9.
68. Lin CC, Moseley AM, Refshauge KM, Haas M, Herbert RD. Effectiveness of joint mobilisation after cast immobilisation for ankle fracture: a protocol for a randomised controlled trial [ACTRN012605000143628]. BMC Musculoskelet Disord 2006;7:46.
69. Critchley DJ, Ratcliffe J, Noonan S, Jones RH, Hurley MV. Effectiveness and cost-effectiveness of three types of physiotherapy used to reduce chronic low back pain disability: a pragmatic randomized trial with economic evaluation. Spine (Phila Pa 1976) 2007;32:1474-81.
70. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655.
71. Canter PH, Coon JT, Ernst E. Cost-effectiveness of complementary therapies in the United Kingdom—a systematic review. Evid Based Complement Altern Med 2006;3:425-32.
72. Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG. A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. Ann Intern Med 2003;138:898-906.
73. Coon JT, Ernst E. A systematic review of the economic evaluation of complementary and alternative medicine. Perfusion 2005;18:202-14.
74. Herman PM, Craig BM, Caspi O. Is complementary and alternative medicine (CAM) cost-effective? A systematic review. BMC Altern Med 2005;5:11.
75. Lin CWC, Haas M, Maher CG, Machado LAC, van Tulder MW. Cost-effectiveness of general practice care for low back pain: a systematic review. Eur Spine J 2011;20:1012-23.
76. Lin CWC, Haas M, Maher CG, Machado LAC, van Tulder MW. Cost-effectiveness of guideline-endorsed treatments for low back pain: a systematic review. Eur Spine J 2011;20:1024-38.
77. Van Der Roer N, Goossens MEJB, Evers SMAA, van Tulder MW. What is the most cost-effective treatment for patients with low back pain? A systematic review. Best Pract Res Clin Rheumatol 2005;19:671-84.
78. White AR, Ernst E. Economic analysis of complementary medicine: a systematic review. Complement Ther Med 2000; 8:111-8.
79. Herman PM, Poindexter BL, Witt CM, Eisenberg DM. Are complementary therapies and integrative care cost-effective? A systematic review of economic evaluations. BMJ Open 2012;2(5):e001046.
80. Lewis R, Williams N, Matar HE, et al. The clinical effectiveness and cost-effectiveness of management strategies for sciatica: systematic review and economic model. Health Technol Assess 2011;15:1-578.
81. Michaleff ZA, Lin CW, Maher CG, van Tulder MW. Spinal manipulation epidemiology: systematic review of cost effectiveness studies. J Electromyogr Kinesiol 2012;22: 655-62.

Appendix 1.

Medline via Ovid Searched on 25/08/2011.

1	Musculoskeletal Manipulations/	647
2	Manipulation, Orthopedic/	3196
3	Manipulation, Chiropractic/	599
4	Manipulation, Spinal/	947
5	Manipulation, Osteopathic/	275
6	Chiropractic/	2910
7	((orthopaedic or orthopedic or chiropract$ or chirother$ or osteopath$ or spine or spinal or vertebra$ or craniocervical or craniosacral or "cranio sacral" or cervical or lumbar or occiput or invertebral or thoracic or sacral or sacroilial or joint$) adj3 (manipulat$ or adjustment$ or mobilis$ or mobiliz$ or traction$)).tw.	3748
8	((manual or manipulat$ or mobilis$ or mobiliz$) adj (therap$ or intervention$ or treat$ or rehab$)).tw.	2087
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	10834
10	Osteopathic Medicine/	2395
11	osteopath$.tw.	3382
12	chiropractic$.tw.	2684
13	chirother$.tw.	16
14	10 or 11 or 12 or 13	6949
15	9 or 14	14942
16	"friction massage$".tw.	22
17	naprapath$.tw.	13
18	Rolfing.tw.	17
19	"myofascial release".tw.	53
20	"Bowen technique".tw.	5
21	"apophyseal glide$".tw.	7
22	"bone setting".tw.	47
23	bonesetting.tw.	14
24	"body work$".tw.	103
25	"high-velocity low-amplitude".tw.	94
26	HVLA.tw.	21
27	((Maitland or Kaltenborn or Evejenth or Evjenth or Mulligan or McKenzie or Cyriax or Mills or Mennell or Stoddard) adj3 (manipulat$ or adjustment$ or mobilis$ or mobiliz$ or traction$)).tw.	17
28	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	386
29	15 or 28	15151
30	meta.ab.	37484
31	synthesis.ab.	356691
32	literature.ab.	333797
33	randomized.hw.	385278
34	published.ab.	229952
35	meta-analysis.pt.	30214
36	extraction.ab.	106463
37	trials.hw.	241415
38	controlled.hw.	476605
39	search.ab.	111279
40	medline.ab.	37563
41	selection.ab.	186391
42	sources.ab.	136598
43	trials.ab.	231023
44	review.ab.	521671
45	review.pt.	1668378
46	articles.ab.	43106
47	reviewed.ab.	273309
48	english.ab.	34846
49	language.ab.	55323
50	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	3593074
51	comment.pt.	449950
52	letter.pt.	723862
53	editorial.pt.	282269
54	Animals/	4854330
55	Humans/	12014638
56	54 and 55	1282233
57	54 not 56	3572097

(continued on next page)

58	51 or 52 or 53 or 57	4613893
59	50 not 58	3118764
60	29 and 59	3786
61	meta-analysis.mp,pt.	47915
62	review.pt.	1668378
63	search$.tw.	167947
64	61 or 62 or 63	1800589
65	29 and 64	1754
66	60 or 65	3869
67	randomized controlled trial.pt.	314563
68	controlled clinical trial.pt.	83211
69	randomized.ab.	220397
70	placebo.ab.	127540
71	drug therapy.fs.	1488387
72	randomly.ab.	159149
73	trial.ab.	227916
74	groups.ab.	1056224
75	67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	2752777
76	exp animals/not humans.sh.	3654092
77	75 not 76	2335094
78	29 and 77	2268
79	exp Cohort Studies/	1124315
80	cohort$.tw.	181429
81	controlled clinical trial.pt.	83211
82	Epidemiologic Methods/	27602
83	limit 82 to yr="1971-1988"	9410
84	79 or 80 or 81 or 83	1268588
85	29 and 84	1737
86	66 or 78 or 85	5540
87	interview$.mp.	191377
88	experience$.mp.	552122
89	qualitative.tw.	86147
90	qualitative research/	11344
91	87 or 88 or 89 or 90	772947
92	29 and 91	1194
93	86 or 92	6056
94	Economics/	26136
95	exp "costs and cost analysis"/	159102
96	economics, dental/	1829
97	exp "economics, hospital"/	17368
98	economics, medical/	8493
99	economics, nursing/	3851
100	economics, pharmaceutical/	2258
101	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	343421
102	(expenditure$ not energy).ti,ab.	14521
103	value for money.ti,ab.	654
104	budget$.ti,ab.	14687
105	94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104	457195
106	((energy or oxygen) adj cost).ti,ab.	2340
107	(metabolic adj cost).ti,ab.	607
108	((energy or oxygen) adj expenditure).ti,ab.	13432
109	106 or 107 or 108	15754
110	105 not 109	453621
111	letter.pt.	723862
112	editorial.pt.	282269
113	historical article.pt.	278980
114	111 or 112 or 113	1272089
115	110 not 114	428994
116	Animals/	4854330
117	Humans/	12014638
118	116 not (116 and 117)	3572097
119	115 not 118	404419
120	29 and 119	562
121	93 or 120	6232