OPEN ACCESS

GAVIN PUBLISHERS

Journal of Orthopedic Research and Therapy

Kim CG, et al. J Orthop Ther: JORT-1119.

Research Article

DOI: 10.29011/2575-8241. 001119

Economic Evaluation of Manual Therapy for Musculoskeletal Diseases: A Systematic Review and Narrative Synthesis of Evidence

Chang-Gon Kim[1], Ka-Na Kim[2], Byung-Cheul Shin[3], Youn-Suk Ko[4], Tae-Yong Park[5], Won-Bae Ha[1], Jung-Han Lee[1*]

[1]Department of Rehabilitation Medicine of Korean Medicine, College of Korean Medicine, Won-Kwang University, Iksan, South Korea

[2]Department of Neuropsychiatry, College of Korean Medicine, Kyung-Hee University, Seoul, South Korea

[3]Third Division of Clinical Medicine, School of Korean Medicine, Pusan National University, Pusan, South Korea

[4]Department of Rehabilitation Medicine of Korean Medicine, College of Korean Medicine, Woo-Suk University, Wanju, South Korea

[5]Institute for Integrative Medicine, Catholic Kwandong University International St. Mary's Hospital, Incheon, South Korea

[*]**Corresponding author:** Jung-Han Lee, Department of Rehabilitation Medicine of Korean Medicine, College of Korean Medicine, Won-Kwang University, 460 Iksan-daero, Iksan 570-749, South Korea. Tel: +82-638592807; Email: milpaso@wku.ac.kr

Citation: Kim CG, Kim KN, Shin BC, Ko YS, Park TY, et al. (2018) Economic Evaluation of Manual Therapy for Musculoskeletal Diseases: A Systematic Review and Narrative Synthesis of Evidence. J Orthop Ther: JORT-1119. DOI: 10.29011/2575-8241. 001119

Received Date: 01 October, 2018; **Accepted Date:** 09 October, 2018; **Published Date:** 15 October, 2018

Abstract

Objectives: The aim of this study was to systematically review economic evaluations of manual therapy relevant to other interventions used for the management of musculoskeletal diseases.

Methods: We searched clinical and economic electronic databases and the reference list of related systematic reviews and included studies up to 2 February 2017. Two reviewers independently selected studies for inclusion and performed the risk of bias assessment by the Cochrane and the Drummond checklist and extracted data independently. To make comparisons, we converted the reported mean costs to the United States dollar (USD) 2015 and used a single willingness to pay threshold of $26,963/QALY announced by the National Evidence-based healthcare Collaborating Agency.

Results: We screened 3,327 economic evaluation-related references and included a total of 18 randomized controlled trials studies. The economic evaluation was conducted as a comparison of the effectiveness of manual therapy intervention with other alternatives in pain reduction. Manual therapy techniques were more cost-effective for improving low back and shoulder pain and lateral epicondylalgia than spinal stabilization, general practitioner care, injection or etc. Moreover, manual therapy was dominant than general practitioner care, physiotherapy, self-management program, traction therapy in improving neck, musculoskeletal chest pain, osteoarthritis of the hip or knee, cervical spondylotic radiculopathy, and hand injury.

Conclusions: In ten out of 18 studies manual therapy was cost-effective, in five out of 10 studies manual therapy was dominant in the treatment of musculoskeletal diseases. This may indicate some economic value of manual therapy compared with other interventions. However, there is an overall lack of evidence as to the economic aspects of the use of manual therapy in the context of musculoskeletal disease treatment. Further well-organized research is needed to make more definitive conclusions and effective recommendations for policy making.

Keywords: Economic Evaluation; Manual Therapy; Musculoskeletal Diseases; Systematic Review

Introduction

Manual therapy is a nonsurgical conservative treatment that is defined as the delivery of manually applied forces using hands on the patient's body for treating, diagnosing, and assessing a variety of diseases [1,2]. This technique is usually applied on soft tissues and joints, and can be used separately or in combination with other treatments [3]. Manual therapy is comprised of different techniques such as manipulation, mobilization, rehabilitative exercises, static stretching, myofascial release techniques, muscle

energy techniques, and other adjunctive treatments [4-7]. The use of manual therapy for musculoskeletal diseases such as neck pain, headache, and low back pain has been recommended worldwide by clinical practice guidelines [8-10]. Musculoskeletal diseases are a serious health problem affecting almost a quarter of the world's population [11,12]. They are prevalent and lead to huge healthcare costs [13]. There are considerable differences in terms of definitions, localizations, causes, and medical care strategies of musculoskeletal diseases [14,15]. Microscopic damage accumulates in certain parts of the body such as muscles, ligaments, tendons, intervertebral discs, cartilage, bone, or related nerves, and blood vessels and can cause acute, recurrent, continuous, or chronic pain or dysfunction [3]. Musculoskeletal issues can occur in various anatomical regions such as the neck, shoulder, elbow, wrist, hand, back, hip, knee, ankle, and foot [16]. In many cases, they affect well-being, and quality of life [17]. Several risk factors have been identified such as occupational exposure, state of education, psychosocial features (anxiety, emotions, and stress), cognitive functioning, and non-adaptive behaviors (smoking, gender, and age) [14,15].

Previous studies have provided sufficient evidence on the use of manual therapy in terms of its effectiveness and safety, but there is insufficient evidence as to its cost-effectiveness [18-34]. Economic evaluations investigate the value for money of health care interventions. The costs and effectiveness of certain interventions compared to others provides insight into the value of a health care intervention. For patients, policy makers, and health care providers this information is important to determine whether or not to compensate, provide, or obtain a specific intervention [35]. Therefore, a comprehensive review to identify and evaluate trial-based economic evidence for manual therapy relative to other alternative interventions used for musculoskeletal diseases is necessary. Although the subject has been reviewed by Tsertsvadze (2014) in a search up to February 2013, the present study extended the review by including new studies published since the completion of the Tsertsvadze (2014) report. Furthermore, we added information from Korean and Chinese databases, since Chuna manual therapy (Korean manual therapy) and Tuina (Chinese manual therapy) are widely used in the treatment of musculoskeletal diseases in Korea and China [36,37]. The purpose of this study was to conduct a systematic review and narrative synthesis of the evidence in randomized controlled trial-based economic evaluations of manual therapy in the treatment of musculoskeletal diseases.

Methods

Search Strategy

The protocol of this review was previously published as a BMJ report [38] (http://bmjopen.bmj.com/content/bmjopen/6/5/e010556.full.pdf) The first step in performing the survey was the review of applicable existing evidence. To conduct a comprehensive survey of the evidence, we performed a systematic review with narrative synthesis. Here, it is reported in full systematic review and has been updated to include studies published up to 2 February 2017 using following health economic, medical, science electronic databases: Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Econlit, Mantis, Index to Chiropractic Literature, Science Citation Index, Social Science Citation Index, the Allied and Complementary Medicine Database (AMED), National Health Service Database of Abstracts of Reviews of Effects (NHS DARE), National Health Service Health Technology Assessment Database (NHS HTA), National Health Service Economic Evaluation Database (NHS EED), and CENTRAL; five Korean medical databases, including Oriental Medicine Advanced Searching Integrated System (OASIS), Research Information Service System (RISS), DBPIA, Korean Traditional Knowledge Portal (KTKP), and KoreaMed; and three Chinese databases, including China National Knowledge Infrastructure (CNKI), VIP, and Wanfang. In addition, we have also investigated grey literature for economic evaluations including the sites of the following organization: Canadian Institute for Health Information (CIHI), Canadian Institute of Health Research (CIHR), National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Tufts Medical Center Cost-effectiveness Analysis Registry, Agency for Healthcare Research and Quality and National Institute for Health Research Health Technology Assessment program.

The full search strategy developed for Medline is shown in (Table 1). Similar search strategy was applied to other databases. The reference catalog of related systematic reviews and included studies were also searched. Search terms were limited to title heading and free-text terms associated with manual therapy. We did not include broader terms like "physiotherapy". Because early tests suggested that the amount of the literature recognized using such an extensive search strategy would be unmanageable. We did not include a condition terms to make the search openly as possible. No publication year and language restriction was applied. The search results were updated on February 2, 2017.

1	"Musculoskeletal Manipulations" [Mesh] or "Chiropractic" [Mesh] or "Osteopathic Medicine" [Mesh]
2	(orthopaedic [TIAB] or orthopedic [TIAB] or chiropract* [TIAB] or chirother* [TIAB] or osteopath* [TIAB] or spine [TIAB] or spinal[TIAB] or vertebra* [TIAB] or craniocervical [TIAB] or craniosacral [TIAB] or "cranio sacral" [TIAB] or cervical [TIAB] or lumbar [TIAB] or occiput [TIAB] or invertebral [TIAB] or thoracic [TIAB] or sacral [TIAB] or sacroilial [TIAB] or joint* [TIAB]) AND (manipulat* [TIAB] or adjustment* [TIAB] or mobilis* [TIAB] or mobiliz* [TIAB] or traction* [TIAB])
3	(manual [TIAB] or manipulat* [TIAB] or mobilis* [TIAB] or mobiliz* [TIAB]) AND (therap* [TIAB] or intervention* [TIAB] or treat* [TIAB] or rehab* [TIAB])
4	osteopath* [TIAB] or chiropractic* [TIAB] or chirother* [TIAB] or "friction massage*" [TIAB] or naprapath* [TIAB] or Rolfing [TIAB] or "myofascial release" [TIAB] or "Bowen technique" [TIAB] or "apophyseal glide*" [TIAB] or "bone setting" [TIAB] or bonesetting [TIAB] or "body work*" [TIAB] or "high-velocity low-amplitude" [TIAB] or HVLA[TIAB] or Maitland [TIAB] or Kaltenborn [TIAB] or Evejenth [TIAB] or Evjenth [TIAB] or Mulligan [TIAB] or McKenzie [TIAB] or Cyriax [TIAB] or Mills [TIAB] or Mennell [TIAB] or Stoddard [TIAB]
5	1 OR 2 OR 3 OR 4
6	Economics [Mesh: No Exp] or "costs and cost analysis" [Mesh] or "economics, dental" [Mesh] or "economics, hospital" [Mesh] or "economics, medical" [Mesh] or "economics, nursing"[Mesh] or "economics, pharmaceutical" [Mesh] or economic* [TIAB] or cost [TIAB] or costs [TIAB] or costly[TIAB] or costing [TIAB] or price [TIAB] or prices [TIAB] or pricing [TIAB] or pharmacoeconomic* [TIAB] or (expenditure* [TIAB]) NOT energy [TIAB] or value for money [TIAB] or budget* [TIAB]
7	"Randomized Controlled Trial" [PT] OR trial* [TI] OR groups [TIAB] OR placebo* [TIAB] OR random* [TIAB]
8	#5 AND #6 AND #7

Table 1: Search Strategy for Medline via PubMed.

Study Selection

Two independent reviewers (CGK and KNK) screened titles and abstracts of all searched studies and selected studies through a full text review, if they meet the eligibility criteria. Any disagreements between the two reviewers were resolved by discussion. Another reviewer (JHL) was consulted if necessary [39] We included English and Chinese-language full economic evaluation studies (cost-effectiveness analysis, and cost-utility analysis) based on Randomized Controlled Trials (RCTs). This review included full-text publications of RCTs that evaluated the cost-effectiveness and/or cost-utility of manual therapy (manipulation, mobilization, static stretching, chiropractic care, muscle energy techniques alone or in combination) compared with alternative interventions used for the management of musculoskeletal diseases. Studies describing the use of any manual therapy in musculoskeletal disease treatment, such as osteopathic spinal manipulation, Physiotherapy (PT) manipulation, chiropractic manipulation, and mobilization techniques with or without other treatments were included. Manual therapy is defined as the delivery of manually applied forces using the intended procedure to improve the quality and range of motion of the target joint and soft tissues [40] No limitations regarding the duration of the treatment, comparison of two or more different interventions, and combinations of treatment or multimodality care were imposed. The control group included placebo, waiting list, no treatment, or usual General Practitioner (GP) care. Patients with musculoskeletal diseases, such as muscles, ligaments, tendons, intervertebral discs, cartilage, and bone were included. They can be categorized as spinal (neck pain, back pain, low back pain, and sciatica), upper extremity (adhesive capsulitis, shoulder disorders, lateral epicondylitis, and carpal tunnel syndrome), lower extremity (osteoarthritis, and ankle sprain), and other (musculoskeletal chest pain) disorders.

We excluded studies in which manual therapy was used to treat acute injuries such as fractures and dislocations (bone realignment), except when it was applied for rehabilitation purposes. Studies reporting only costs without an analysis of efficacy and effectiveness were excluded. Studies reporting other types of economic analysis (cost-consequence analysis) were also excluded, since they presented an array of different outcomes and cost measures. Studies that were not economic evaluations, did not involve relevant interventions, were non-randomized controlled trials, and that had insufficient information to calculate the incremental Cost-Effectiveness Ratios (ICERs) for Cost-Effectiveness Analysis (CEA) or Cost-Utility Analysis (CUA) were excluded. Lastly, abstracts, commentaries, letters, protocol studies, and systematic and other reviews were excluded.

Data Extraction

Data from the included studies was independently extracted by two independent reviewers (CGK and KNK). Any disagreements between the two reviewers were resolved by discussion with a third reviewer (JHL). Publications relevant to the included studies

(published protocol or effectiveness consequences studies) are listed in (Table 2) and were used to support these analyses. The results were organized by the condition and the type of manual therapy. A standard data extraction sheet was used to collect information regarding study characteristics (publication year, name of author, country, sample size, and follow-up duration), types of participants (condition, age, sex, and inclusion, and exclusion criteria), perspective type, cost methods, discounting, pain and disability scores, quality of life measures, quality adjusted life-years (QALYs), costs, ICERs, types of interventions and comparisons, type of economic analysis (CEA, or CUA), and currency of study which was the primary outcome. In studies where one treatment was associated with cost reduction and found to produce greater effects compared to the alternative treatment, the treatment is said to be dominant and the description of an ICER is not needed. In this case, when presented graphically, the ICER would be plotted in the south-east quadrant of the cost-effectiveness plane [41].

Included studies	Related publications
Williams, et al. [42]	Williams, et al. [43]
Yu, et al. [44]	None
Bosmans, et al. [45]	Pool, et al. [46,47]
Korthals-de Bos, et al. [48]	Hoving, et al. [49]
Lewis, et al. [50]	Dziedzic, et al. [51]
Van Dongen, et al. [52]	Groeneweg, et al. [53]
Stochkendahl, et al. [54]	Stochkendahl, et al. [55,56]
Critchley, et al. [57]	None
Neimisto, et al. [58]	Niemisto, et al. [59]
Rivero-Arias, et al. [60]	Frost, et al. [61]
UK BEAM trial team [62]	Brealey, et al. [63], UK BEAM Trial Team [64]
Whitehurst, et al. [65]	Hay, et al. [66]
Bergman, et al. [67]	Berman, et al. [68-70]
Coombes, et al. [71]	Coombes, et al. [72]
Zhang, et al. [73]	None
Lin, et al. [74]	Lin, et al. [75]
Pinto, et al. [76]	Abbott, et al. [40,77], Pinto, et al. [78]
Hu, et al. [79]	None
BEAM: Back pain exercise and manipulation	

Table 2: Publications Relevant to the Included Studies.

Quality Assessment

Assessment of the Risk of Bias: Two independent reviewers (CGK and KNK) assessed the risk of bias of the included studies according to a clinical outcomes assessment tool using 12 criteria recommended by the Cochrane Back Review Group [80] The quality of each trial in terms of the risk of bias was rated as low risk, high risk, or unclear. Studies that met at least 6 of the 12 criteria were considered low risk, while those that met 5 or fewer criteria were rated high risk [80] In support of this system, the previous studies have indicated that studies with low methodological quality (higher risk of bias) tend to overestimate the treatment effects [81,82] We resolved any disagreement through discussion or consultation with a third reviewer (JHL) if necessary.

Methodological Quality of the Economic Evaluations: Studies involving economic evaluations were evaluated using a recommended tool with the Drummond checklist (10 items) for the critical appraisal of the economic evaluation [83] The response options for each item are yes, no, not clear or not appropriate. We resolved any disagreement via discussion or consultation with a third reviewer (JHL) if necessary. This enabled the investigators to develop a qualitative assessment of the complete study.

Data Analysis

For data analysis and demonstration, results of studies were grouped first according to condition and then by the type of manual therapy performed. The results are summarized in tables and in the text. Moreover, regardless of the interventions investigated, studies reporting ICERs using general outcomes (cost per QALYs gained) were compared after adapting to cost differences across countries and time. To make comparisons across countries and years, we converted the reported mean costs to the USD 2015. An international exchange rate based on Purchasing Power Parities (PPP) was used to convert cost estimates to the USD, and country-specific Gross Domestic Product (GDP) deflators were used to convert cost estimates to 2015 equivalents. GDP and PPP data were taken from the World Economic Outlook Database (http://www.imf.org/external/data.htm) and PPP Database (http://www.oecd.org/std/prices-ppp/urchasingpower paritiespppsdata.htm). (Table 3) The threshold for the national health policy of the Republic of Korea has not been formally announced; however, based on the contents of the Asian collaboration on cost-effectiveness in health care decision making (2012) announced by the National Evidence-based healthcare Collaborating Agency (www.neca.re.kr) and preceding articles, we used a single Willingness to Pay (WTP) threshold of $26,963/QALY as an indicator of cost-effectiveness. That is, if a treatment resulted in an ICER that was lower than the threshold when compared to an alternative, the treatment was considered relatively cost-effective.

	Original Currency	Exchange Rate
Williams, et al. [42]	£1999-2000	2.12
Yu, et al. [44]	元2005	0.24
Bosmans, et al. [45]	€2004	2.15
Korthals-de Bos, et al. [48]	€2000	2.16
Lewis, et al. [54]	£2003	2.39

van Dongen, et al. [50]	€2010	1.37
Stochkendahl, et al. [54]	€2014	1.33
Critchley, et al. [57]	£2003-2004	1.94
Niemisto, et al. [58]	$2002	1.24
Rivero-Arias, et al. [60]	£2004	1.94
UK BEAM* trial team [62]	£2010	2.13
Whitehurst, et al. [65]	£2001-2002	2.02
Bergman, et al. [67]	€2000	1.98
Coombes, et al. [71]	AU$†2013	1.40
Zhang, et al. [73]	元2006	0.22
Lin, et al. [74]	AU$2005	4.37
Pinto, et al. [76]	NZ$‡2009	1.23
Hu, et al. [79]	元2009	0.19
*USD: United States dollar †AU$: Australian dollar ‡NZ$: New Zealand dollar		

Table 3: Exchange Rate of Original Currency and 2015 USD*.

Results

Search Results

A total of 3,327 references were screened for the economic evaluation systematic review, of which 142 passed at the title and abstract screening level and were considered for full-text review. One-hundred twenty-four of the 142 studies were excluded at the full-text level. They included the following: studies that reported information on costs (n = 28) only, cost-consequence studies (n = 11), CUAs where not enough information was provided to calculate the ICER (n = 2), studies that were not economic evaluations (n = 3), systematic and other reviews (n = 38), studies without relevant intervention (n = 15), abstracts/commentaries/ letters (n = 8), protocols (n = 18), and studies that were not randomized-controlled (n = 1). (Figure 1) provides all of the details of the search and exclusion processes. The remaining 18 randomized controlled trials included in the systematic review, were as follows: Williams, et al. [42,43] Yu, et al. [44] Bosmans, et al. [45-47] Korthals-de Bos, et al. [48,49] Lewis, et al. [50,51] van Dongen, et al. [52,53] Stochkendahl, et al. [54-56] Critchley, et al. [57] Niemisto, et al. [58,59] Rivero-Arias, et al. [60,61] the UK Back Pain Exercise and Manipulation (BEAM) trial team, [62-64] Whitehurst, et al. [65,66] Bergman, et al. [67-70] Coombes, et al. [71,72] Zhang, et al. [73] Lin, et al. [74,75] Pinto, et al. [76-79] and Hu, et al. [84]

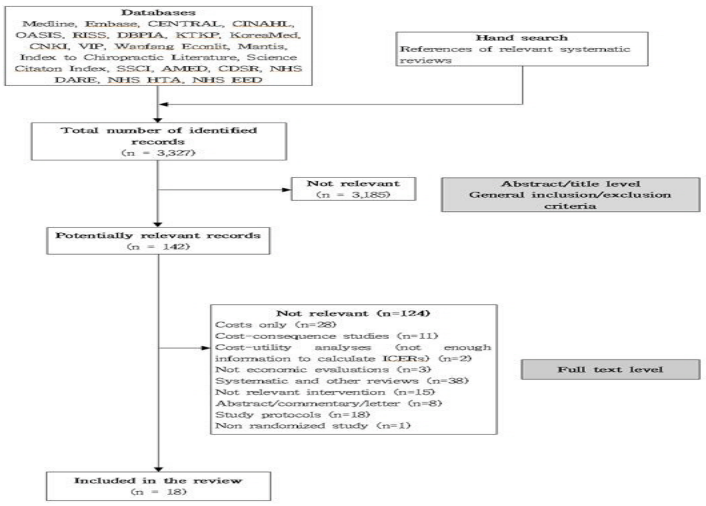

Figure 1: Flowchart of the study selection progress.

Study Characteristics

(Table 4) reports the basic study, participant, perspective type of methods, intervention, outcome characteristics, and analysis of the 18 included studies. The included studies were conducted in China, [44,73,84] Denmark, [54] New Zealand, [76] the United Kingdom, [42,50,57,60,62,65] the Netherlands, [45,48,52,67] Finland, [58] and Australia [71,74] 15 studies were published in English, 3 studies were published in Chinese. The publication year of research ranged from 2003 to 2016. The size of sample ranged from 50 [73] to 1334 [62] participants. The follow-up duration across reports ranged from 1 [44] to 24 [58] months. The participants of included study mean age ranged from 29.35 [73] to 66.6 [76] years. The participants presented with spinal (low and upper back, neck) pain, [42] cervical spondylotic radiculopathy, [44] neck pain, [45,48,50,52] musculoskeletal chest pain, [54] low back pain, [57,58,60,62,65] shoulder pain, [66] lateral epicondylalgia, [71] hand injury, [73] ankle pain, [74] and osteoarthritis of the knee/hip or knee [76,84] Participants with musculoskeletal pain were included in all of the studies except for patients with spinal and shoulder pathology, severe osteoporosis, hemophilia, spinal infection, rheumatoid arthritis, malignancies, pregnancy and psychiatric disease. In the reviewed reports, interventions whose principal components included manual therapy techniques (manipulation, stabilizing, and mobilization) were compared with acupuncture, [84] traction therapy, [44] injection (saline and corticosteroid), [71] usual GP care, [42,48,62,67,76] GP advice, [58] physiotherapist advice, [60] self-management programs, [54] pain management programs (guidance function training, back pain education, strengthening, stretching, aerobic exercise), [57,65,73] exercise, [45,76] PT (traction, massage, postural relaxation, walking exercises, stretching), [48,52,74] or advice and exercise [50] Most interventions lasted from 6 to 12 weeks. More details on

the interventions analyzed in the included studies are provided in (Table 1).

Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Spinal pain (low back, upper back, and/or neck)				
Williams [42] 2004 UK National Health Service	Size: 201 (randomized), 136(analyzed) Age (mean): NR* Male (%): NR	Direct medical costs: GP† and outpatient consultations, hospital stay, investigations, prescribing Direct non-medical costs: NA‡ Indirect costs: NA Discounting: None	Intervention 1: OSM§ + 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 EQ-5D¶) ICER#, Last follow-up: 6 months
Cervical spondylotic radiculopathy				
Yu [44] 2008 China Societal	Size: 69 (randomized and analyzed) Age (mean): 54.44 Male (%): 26.08	Direct medical costs: treatment and registration fees Direct non-medical costs: transportation costs Indirect costs: loss of working time Discounting: None	Intervention 1: Tuina manipulative therapy group [1time/2days] Intervention 2: Traction therapy group [1time/1day] Duration: 2 weeks	ICER (based on perceived recovery), Last follow-up: 4 weeks
Neck pain				
Bosmans [45] 2011 The Netherlands Societal	Size: 146 (randomized and analyzed) Age (mean): 45 Male (%): 40	Direct medical costs: primary care (GP, SMT**, BGA††, massage, 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	Intervention 1: SMT (manipulation using passive movement of a joint beyond its active and passive limit of motion with a localized thrust of small amplitude to regain motion) [6 sessions] Intervention 2: BGA (gradually increasing exercise program) [18 sessions] Duration: 6 weeks	Mean QALY ICER (based on QALY, pain; perceived recovery; NDI§§), Last follow-up: 12 months
Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up

Korthals-de Bos [48] 2003 The Netherlands Societal	Size: 183 (randomized), 178 (analyzed) Age (mean): 45 Male (%): 40	Direct medical costs: GP, PT‖, SMT, outpatient appointments, hospitalization, 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	Intervention 1: SMT (combination of techniques described by Cyriax, Kaltenborn, Maitland, and Mennel using hands-on muscular and articular mobilization techniques, coordination or stabilization techniques, and joint mobilization) [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 EQ-5D, pain; NDI), Last follow-up: 12 months
Lewis [50] 2007 UK National Health Service and Societal	Size: 350 (randomized), 346 (analyzed) Age (mean): 51 Male (%): 37	Direct medical costs: GP consultations, study intervention sessions, outpatient attendance Direct non-medical costs: patient expenses Indirect costs: absenteeism from paid work Discounting: None	Intervention 1: A & E## [8 sessions] Intervention 2: A & E + SMT (passive/ active assisted hands-on movements, joint and soft tissue mobilization 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 EQ-5D; NPQ†††), Last follow-up: 6 months
Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up

van Dongen [52] 2016 The Netherlands, Societal	Size: 181 (randomized and analyzed) Age (mean): 48.9 Male (%): 38.1	Direct medical costs: intervention costs of MTU‡‡‡ or PT costs, healthcare utilization included care by a healthcare provider Direct non-medical costs: prescribed and over-the-counter medication. healthcare utilization informal care Indirect costs: absenteeism, unpaid productivity losses Discounting: None	Intervention 1: MTU group (combination of rolling and sliding, or rocking and gliding, in the joints of the spine and extremities) [≤6 sessions, 1time/1-2weeks] Intervention 2: PT group (active exercises, muscle stretching, manual traction, and massage) [≤9 sessions, 1-2times/1week] Duration: 6 weeks	Mean QALY ICER (based on mean QALY, recovery, NDI-DV§§§), Last follow-up: 12 months
Musculoskeletal chest pain				
Stochkendahl [54] 2015 Denmark Societal	Size: 115 (randomized and analyzed) Age (mean): 51.1 Male (%): 58.3	Direct medical costs: intervention costs, additional visits to mainstream healthcare and complementary and alternative medicine providers and hospital contacts Direct non-medical costs: prescriptive and non-prescriptive drugs Indirect costs: NR Discounting: None	Intervention 1: Chiropractic treatment (high-velocity, low-amplitude manipulation directed toward the thoracic and/or cervical spine, joint mobilization, soft tissue techniques) [≤10 sessions] Intervention 2: Self-management (consultation consisting of reassurance, advice and individual instructions regarding posture and 2 to 3 home exercises) [1 sessions] Duration: 4 weeks	Mean QALY (based on quality of life score EQ-5D, SF-36‖‖) ICER, Last follow-up: 12 months
Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Low Back pain				

Critchley [57] 2007 UK National Health Service	Size: 212 (randomized), 148 (analyzed) Age (mean): 44 Male (%): 35.8	Direct medical costs: healthcare visits, hospital stays, staff time, inpatient procedures, investigations, medication Direct non-medical costs: NA Indirect costs: NA Discounting: 3.50%	Intervention 1: Individual PT (joint manipulation, mobilization, massage, back care advice, individual exercises including trunk muscle retraining) [12 sessions] Intervention 2: Spinal stabilization PT (transverses abdominis and lumbar multifidus muscle training, exercise for spinal stability) [8 sessions] Intervention 3: Pain management [8 sessions] Duration: NR	Mean QALY (based on quality of life score EQ-5D) ICER, Last follow-up: 18 months
Neimisto [58] 2005 Finland Societal	Size: 204 (randomized), 138 (analyzed) Age (mean): 37 Male (%): 46	Direct medical costs: visits to physician, PT 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) [4 sessions] Intervention 2: GP advice (booklet, advice on exercise, muscle stretch) [1 session] Duration: 4 weeks	ICER (based on pain and ODI¶¶¶ scores), Last follow-up: 24 months
Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up

Rivero-Arias [60] 2006 UK National Health Service and Societal	Size: 286 (randomized and analyzed) Age (mean): 41 Male (%): 47.5	Direct medical costs: NHS### costs (intervention, GP visits, hospitalizations, 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	Intervention 1: PT (joint manipulation, mobilization, massage, stretching, spinal mobility and strengthening exercise, heat/cold therapy) + advice to remain active [5 sessions] Intervention 2: Advice to remain active (back book) [1 session] Duration: NR	Mean QALY (based on quality of life score EQ-5D) ICER, Last follow-up: 12 months
UK BEAM [62] 2004 UK National Health Service	Size: 1334 (randomized), 1287 (analyzed) Age (mean): 43.1 Male (%): 44	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	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) + GP care [9 sessions] Intervention 4: Manipulation + exercise + GP care [9 sessions] Duration: 12 weeks	Mean QALY ICER (based on EQ-5D, RMDQ**** score), Last follow-up: 12 months
Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up

Whitehurst [65] 2007 UK National Health Service	Size: 402 (randomized and analyzed) Age (mean): 41 Male (%): 47	Direct medical costs: treatment sessions (PT and brief pain management), outpatient attendance, inpatient attendance, primary care contacts, other health professionals Direct non-medical costs: NA Indirect costs: NA Discounting: None	Intervention 1: Manual PT (articulatory mobilization, manipulation, or soft tissue techniques, spinal stabilization, back exercise, ergonomic advice, back education) [7 sessions] Intervention 2: Brief pain management (general fitness, exercise for spinal mobility, explanation about pain mechanisms, distress, coping strategies) [2 days course plus clinical tutoring] Duration: NR	Mean QALY ICER (based on EQ-5D, RMDQ score), Last follow-up: 12 months
Shoulder pain				
Bergman [67] 2010 The Netherlands Societal	Size: 150 (randomized), 140 (analyzed, excluding 2) Age (mean): 48 Male (%): 49	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 hospitalization 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	Intervention 1: SMT (high velocity low amplitude manipulation and passive low velocity mobilization 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
Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Lateral epicondylalgia				

Coobmes [71] 2015 Australia Societal	Size: 165 (randomized), 154 (analyzed) Age (mean): 49.7 Male (%): 62	Direct medical costs: intervention costs of medical injection, PT, other Direct non-medical costs: over the counter medication, assistive devices, paid or unpaid labor, transportation Indirect costs: work absence, leisure time loss Discounting: None	Intervention 1: Saline injection (0.5mL of 0.9% isotonic saline) + GP care (advice to avoid activities for 2 weeks, after 2 weeks) [1 session] Intervention 2: Saline injection + PT (MT††††, concentric and eccentric wrist extension exercises, motor control retraining and global upper body strengthening, a daily home exercise program) + GP care [1 session of injection, 8 sessions of PT] Intervention 3: Corticosteroid injection (10mg/mL of triamcinolone acetonide + 1 mL of 1% lignocaine) + GP care [1 session] Intervention 4: Corticosteroid injection + PT + GP care [1 session of injection, 8 sessions of PT] Duration: 10 weeks	Mean QALY (based on quality of life score EQ-5D) ICER, Last follow-up: 12 months
Zhang [73] 2009 China Societal	Size: 50 (randomized and analyzed) Age (mean): 29.36 Male (%): 90	Direct medical costs: rehabilitation costs, hospital-related costs, diagnostic costs of complications Direct non-medical costs: non-hospitalized treatment and medication costs Indirect costs: NR Discounting: None	Intervention 1: Rehabilitation group (routine hand surgery + individual rehabilitation education, rehabilitation treatment program, PT, occupational therapy, stress treatment, psychological treatment) [after surgery 2 times/day] Intervention 2: Control group (routine hand surgery + guidance function training) [NR] Duration: 12 weeks	ICER (based on Tendon total active motion, Minnesota manual dexterity, Purdue pegboard assessment systems), Last follow-up: 3 months
Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Ankle pain				

Lin [74] 2008 Australia Health care system and patient	Size: 94 (randomized), 92 (analyzed) Age (mean): 41.5 Male (%): 54	Direct medical costs: outpatient PT, GP, medical specialists, emergency department, hospitalization, medication, investigations, private health providers Direct non-medical costs: public transport, private vehicle Indirect costs: None Discounting: None	Intervention 1: MT (large amplitude oscillatory anterior-posterior glides of the talus) + PT (exercise, gait retraining, walking aids, advice, ice, elevation, progression if required) [8 sessions] Intervention 2: PT (exercise, gait retraining, walking aids, advice, ice, elevation, progression if required) [5 sessions] Duration: 4 weeks	ICER (based on quality of life AQol‡‡‡‡: QALY), Last follow-up: 6 months
Osteoarthritis of the hip or knee				
Pinto [76] 2013 New Zealand New Zealand health system and Societal	Size: 206 (randomized and analyzed) Age (mean): 66.6 Male (%): 44.7	Direct medical costs: health professionals, public and private hospital use, medications, aids and adaptations, and community service Direct non-medical costs: out-of-pocket costs, transportation costs and informal care Indirect costs: lost earnings, productivity loss Discounting: None	Intervention 1: Usual care (routine care offered by their own GP and other healthcare providers) [9 sessions] Intervention 2: MT + usual care (application of therapist-applied manual forces in procedures intended to modify the quality and range of motion of the target joint and soft tissue structures) [9 sessions] Intervention 3: Exercise therapy + usual care (multi-modal, supervised programme of warm-up/aerobic, muscle strengthening, muscle stretching, and neuromuscular control exercises) [9 sessions] Intervention 4: Combined therapy + usual care (MT + exercise therapy) [9 sessions] Duration: 9 weeks	Mean QALY ICER (based on mean QALY, Western Ontario and McMaster University osteoarthritis index, Outcomes Measures in Rheumatology Clinical Trials - Osteoarthritis Research Society International), Last follow-up: 12 months
Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Osteoarthritis of the knee				

Hu [84] 2012 China NR	Size: 60 (randomized and analyzed) Age (mean): 63.55 Male (%): 16.7	Direct medical costs: intervention costs of Tuina manipulative therapy, acupuncture Direct non-medical costs: None Indirect costs: NA Discounting: None	Intervention 1: Acupuncture group (acupuncture + electroacupuncture) [12 sessions] Intervention 2: Tuina manipulative therapy group (Tuina manipulative therapy like revolving method + knee flexion and extension of passive movement and active exercise) [12 sessions] Duration: 4 weeks	ICER (based on Western Ontario and McMaster University osteoarthritis index), Last follow-up: 4 weeks
*NR: not reported, †GP: general practitioner, ‡NA: not applicable, §OSM: osteopathic manual therapy, ‖QALY: quality-adjusted life year, ¶EQ-5D: European Quality of Life-5 Dimensions, #ICER: incremental cost-effectiveness ratio, **SMT: spinal manual therapy, ††BGA: behavioral graded activity, ‡‡MRI: magnetic resonance imaging, §§NDI: Neck Disability Index, ‖‖PT: physiotherapy, ¶¶NSAIDs: nonsteroidal anti-inflammatory drugs, ##A&E: advice and exercise, ***PSWD: pulsed shortwave diathermy, †††NPQ: Northwick Park Neck Pain Questionnaire, ‡‡‡MTU: manual therapy according to the Utrecht School, §§§DV: Dutch Version, ‖‖‖SF-36: Short Form 36-item Health Survey, ¶¶¶ODI: Oswestry Disability Index, ###NHS: National Health Service, ****RMDQ: Roland-Morris Disability Questionnaire, ††††MT: manual therapy, ‡‡‡‡AQoL: assessment of quality of life				

Table 4: Characteristics of included 18 randomized controlled trials.

Most economical analyses of cost-effectiveness were based on pain intensity (VAS), functional disability, and perceived patient recovery measures. Utilities were measured using European Quality of Life-5 Dimensions (EQ-5D), the six-dimensional health status short form (SF-6D), or the Assessment of Quality of Life (AQOL), and then transformed into QALYs. The perspective of the reports was either societal [44,45,48,50,52,54,58,60,67,71 ,73,76] or from the health care system [42,50,57,60,62,65,74] Most societal perspective studies included direct medical, direct nonmedical and indirect costs with the exception of one report [73] In most studies, discounting was not considered in the context of a short follow-up of 12 months.

Quality of Economic Evaluations

The quality assessment of economic evaluations showing the proportion of items with "yes" on the Drummond checklist is provided in (Table 5). In all studies, the investigation question was clearly devised, with good explanations of the interventions and comparators. Most studies reported all important costs (direct medical, direct nonmedical and indirect) and consequences (efficacy outcome measures). Since costs were not separately itemized for more than half of the research, which data were used to figure out the total costs was not always clear. In all studies, assessment methods of costs and consequences were concluded to be adequate. Since the follow-up of the majority of studies was less than 12 months, there was no need to execute discounting. The ICERs and/or cost-utility ratios (ICURs) were reported in all 18 studies, except for 1 study where details were provided in order calculate this ratio [74] Of the 18 studies reporting ICERs and/or ICURs, 4 studies did not consider the uncertainty of the cost-effectiveness ratio estimation [54,73,74,84] The methods for researching uncertainty included sensitivity analyses, bootstrapping method for confidence intervals, cost-effectiveness plane and cost-effectiveness acceptability curves. 14 studies provided detailed discussion sections by emphasizing the most important issues such as the interpretation of the findings such as uncertainty, main study findings, study strengths and limitations, regularity of the study findings across other similar reports, knowledge gaps, and future directions.

Item number	1	2	3	4	5	6	7	8	9	10	% of yes
Bergman, et al. [67]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	90
Bosmans, et al. [45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Coombes, et al. [71]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	90
Critchley, et al. [57]	Yes	Yes	Yes	Can't tell (costs)	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	80
Hu, et al. [84]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	No	No	70
Korthals-de Bos, et al. [48]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	No	80
Lewis, et al. [50]	Yes	Yes	Yes	No (costs)	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	80
Lin, et al. [74]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	No	No	Yes	70
Niemisto, et al. [58]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	90
Pinto, et al. [76]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Rivero-Arias, et al. [60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Stochkendahl, et al. [54]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	No	Yes	80
UK BEAM trial team [62]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
van Dongen, et al. [52]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	90
Whitehurst, et al. [65]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Williams, et al. [42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Yu, et al. [44]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	No	80
Zhang, et al. [73]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	No	No	90

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

Table 5: The Drummond Checklist for Critical Appraisal of Economical Evaluation [45].

Risk of Bias Assessments

Risk of bias assessments are presented in (Figure 2). In brief, 16 of the 18 included studies were evaluated as having a low risk of bias, [44,45,48,50,52,54,57,58,60,60,65,67,71,74,76,84] whereas 2 studies were found to have a high risk of bias [42,73] as patients and care providers in those studies were not blinded to the intervention type. Thirteen trials reported adequate methods of randomization and treatment allocation concealment. Since the outcomes were self-reported (pain, quality of life, etc.), blinding of assessors was considered not applicable; only except one study referred to outcome assessor blinding. Results of all studies were based on intention-to-treat analyses.

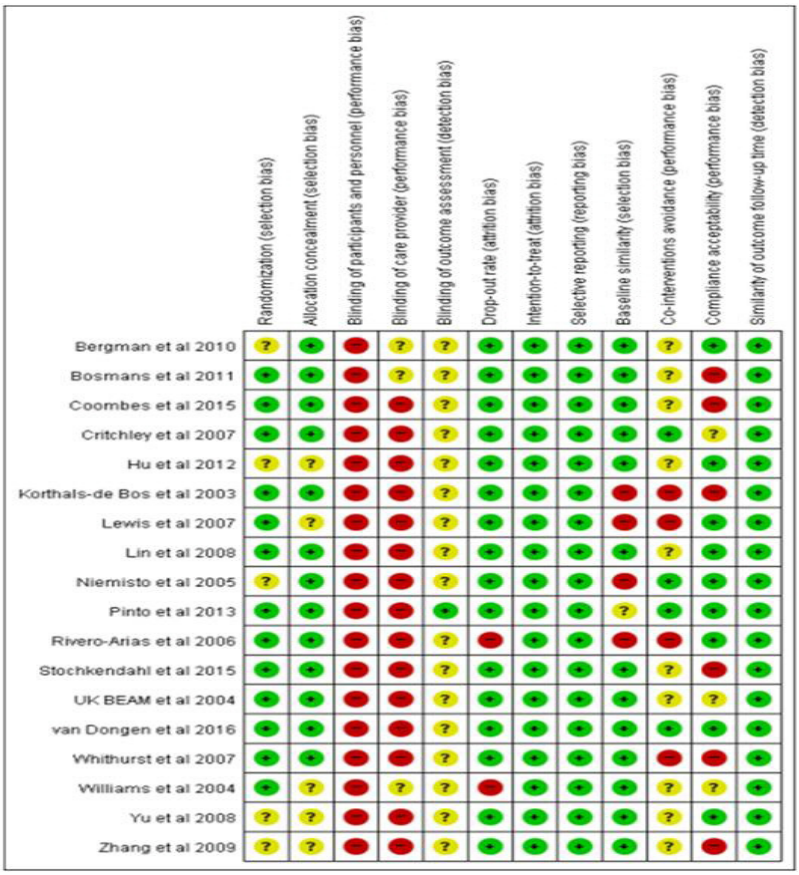

Figure 2: Risk of bias summary.

Cost-Effectiveness And/ Or Cost-Utility of Manual Therapy

Results for CEAs and CUAs of included studies are classified according to condition in the text below (Table 6).

Study ID	Analysis	Outcomes	Mean Costs	Mean Effects (SD)	Costs Difference	ICER*
Spinal pain (low back, upper back, and/or neck)						
Williams [42] 2004 UK	CUA†	EuroQoL EQ-5D‡	OSM§ + usual GP‖ care costs: $643 Usual GP care costs: $457	EQ-5D: 0.717 (0.248) QALY: 0.056 (0.101) EQ-5D: 0.656 (0.289) QALY: 0.031 (0.105)	$186	Cost per QALY¶ gained: $7,471
Cervical spondylotic radiculopathy						
Yu [44] 2008 China	CEA#	perceived recovery	Tuina manipulative therapy group: $168 Traction therapy group: $257	Recovery: 12.17 Recovery (%): 58.94 Recovery: 8.45 Recovery (%): 43.40	-$89	Dominance of Tuina manipulative therapy over traction therapy in terms of perceived recovery
Neck pain						

Bosmans [45] 2011 The Netherlands	CEA, CUA	VAS**, NDI††, perceived recovery, quality of life	SMT‡‡ costs: $1,316 BGA§§ costs: $1,877	VAS: 3.5 (SE 0.31) NDI: 8.3 (SE 0.77) Recovery: 0.76 (SE 0.05) QALY: 0.770 (SE 0.01) VAS: 4.4 (SE 0.31) NDI: 10.6 (SE 0.79) Recovery: 0.78 (SE 0.05) QALY: 0.750 (SE 0.01)	-$561	Cost per unit of outcome improved in: BGA versus SMT Recovery: $27,884 Pain: $623 NDI: $243 Cost per QALY gained: -$27,884
Study ID	Analysis	Outcomes	Mean Costs	Mean Effects	Costs Difference	ICER
Korthals-de Bos [48] 2003 The Netherlands	CEA, CUA	VAS, NDI, perceived recovery, EQ-5D	1. SMT costs: $965 2. PTǁ costs: $2,802 3. GP care costs: $2,980	VAS: 4.2 (2.4) NDI: 7.2 (7.5) Recovery: 71.7 (43) EQ-5D: 0.820 (0.13) VAS: 3.1 (2.9) NDI: 6.3 (8.0) Recovery: 62.7 (37) EQ-5D: 0.790 (0.14) VAS: 4.1 (2.9) NDI: 8.5 (7.4) Recovery: 56.3 (36) EQ-5D: 0.770 (0.16)	1-3: -$2,015 2-3: -$178	Dominance of SMT over GP care and PT in terms of recovery, pain and QALYs GP over PT care Pain: $178 NDI: $80 Dominance of PT over GP care in terms of QALYs
Lewis [50] 2007 UK	CEA, CUA	Disability (NPQ¶¶), EQ-5D	1. A&E## costs: $723 2. SMT + A&E costs: $587 3. PSWD*** + A&E costs: $655	NPQ: 11.5 (15.7) QALY: 0.362 (0.114) NPQ: 10.2 (14.1) QALY: 0.342 (0.114) NPQ: 10.3 (15.0) QALY: 0.360 (0.094)	2-1: -$136 3-1: -$68	Cost per NPQ gained: A&E over SMT $104 Cost per QALY gained: A&E over SMT $7,468
van Dongen [52] 2016 The Netherlands	CEA, CUA	perceived recovery, disability (NDI-DV†††), SF-6D‡‡‡	MTU§§§ group : $3,351 PT group : $3,482	NR NR	-$131 Incremental effects: Recovery: 0.09 NDI-DV (continuous): -1.03 (dichotomous): -0.01 QALY: -0.01	Cost per recovery gained: -$1,413 NDI-DV (continuous): $126 (dichotomous): $10,038 Cost per QALY gained $19,984
Study ID	Analysis	Outcomes	Mean Costs	Mean Effects	Costs Difference	ICER
Musculoskeletal chest pain						

Stochkendahl[54] 2015 Denmark	CUA	EQ-5D, SF-36‖‖	Chiropractic treatment: $4,039 Self-management program: $7,033	EQ-5D: 0.826 SF-36: 0.788 QALY(EQ-5D): 0.811 QALY(SF-36): 0.765 EQ-5D: 0.823 SF-36: 0.774 QALY(EQ-5D): 0.802 QALY(SF-36): 0.756	-$2,994	Dominance of Chiropractic treatment over self-management program in terms of QALYs
Low Back pain						
Critchley [57] 2007 UK	CUA	EQ-5D	1. Individual PT costs: $918 2. Spinal stabilization PT costs: $734 3. Pain management costs: $320	EQ-5D: 0.67 QALY: 0.990 EQ-5D: 0.63 QALY: 0.900 EQ-5D: 0.68 QALY: 1.000	1-2: $184	Cost per QALY gained: $2,043 Pain management dominant over both treatments
Neimisto [58] 2005 Finland	CEA	VAS, ODI, HRQoL¶¶¶ (15D)	NR NR	NR NR	$2,060 Incremental effects: VAS: 4.97 (4.83-5.12) ODI: 1.24 (1.18-1.30)	Cost per VAS gained: $635 Cost per ODI gained: -$97
Rivero-Arias [60] 2006 UK	CUA	EQ-5D	PT costs: $512 Physiotherapist advice cost: $395	EQ-5D: 0.73 (0.25) QALY: 0.740 (0.18) EQ-5D: 0.72 (0.26) QALY: 0.690 (0.23	$117	Cost per QALY gained: $2,324
Study ID	Analysis	Outcomes	Mean Costs	Mean Effects	Costs Difference	ICER
UK BEAM [62] 2004 UK	CUA	EQ-5D	1. GP care Costs: $718 2. GP care + exercise Costs: $1,009 3. GP care +manipulation Costs: $1,151 4. GP care + manipulation +exercise Costs: $978	QALY: 0.618 QALY: 0.635 QALY: 0.659 QALY: 0.651	2-1: $291 3-1: $433 4-1: $260	Cost per QALY gained: $17,091 $9,871 $7,861
Whitehurst [65] 2007 UK	CUA, CEA	Disability (RMDQ### score), EQ-5D	Manual PT Costs: $393 BPM**** Costs: $288	disability(RMDQ): 8.887 QALY: 0.777 disability(RMDQ): 8.553 QALY: 0.755	$105	Cost per RMDQ gained: $316 Cost per QALY gained: $4,805
Shoulder pain						

Bergman [67] 2010 The Netherlands	CEA	Perceived recovery, shoulder pain and disability, general health	SMT + GP care costs: $2,305 GP care costs: $1,097	Recovery: 41% Pain: 5.9 (5.4) Disability: 33.0 (34.6) General health: 0.11 (0.19) Recovery: 35% Pain: 5.2 (5.5) Disability: 20.3 (35.9) General health: 0.08 (0.21)	$1,208	Cost per recovery gained: $241 Cost per pain gained: $1,728 Cost per disability gained: $96 Cost per general health gained: $40,316
Study ID	Analysis	Outcomes	Mean Costs	Mean Effects	Costs Difference	ICER
Lateral epicondylalgia						
Coobmes [71] 2015 Australia	CUA	EQ-5D	1. Saline injection: $124 2. Saline injection +PT: $844 3. Corticosteroid injection: $212 4. Corticosteroid injection + PT: $767	EQ-5D: 0.737 (0.122) QALY: 0.880 (0.092) EQ-5D: 0.744 (0.125) QALY: 0.920 (0.075) EQ-5D: 0.692 (0.175) QALY: 0.873 (0.075) EQ-5D: 0.755 (0.036) QALY: 0.891 (0.084)	2-1: $720 3-1: $88 4-1: $643	Cost per QALY gained $21,046 -$22,772 $163,532
Hand injury						
Zhang [73] 2009 China	CEA	TAM††††, MMDT‡‡‡‡, PPT§§§§	Rehabilitation group : $1,972 Control group: $2,103	TAM: 67.8 MMDT: 77 PPT: 42.5 TAM: 29.3 MMDT: 55 PPT: 31.2	-$131	Dominance of rehabilitation group treatment over control group treatment in terms of TAM, MMDT, PPT
Ankle pain						
Lin [74] 2008 Australia	CUA	Quality of life(AQoLⅡⅡⅡ), activity limitation (LEFS¶¶¶¶)	MT + PT costs: $3,624 PT costs: $2,804	NR NR	$820 Incremental effects: AQoL: 1.3 QALY: -0.09 LEFS: -1.0	Cost per QALY gained: -$9,111
Study ID	Analysis	Outcomes	Mean Costs	Mean Effects	Costs Difference	ICER
Osteoarthritis of the hip or knee						

Pinto [76] 2013 New Zealand	CEA, CUA	SF-12v2, WOMAC ####, OMERACT-OARSI *****	1. Usual care $7,756 2. Manual therapy + usual care: $7,565 3. Exercise therapy +usual care: $8,437 4. Combined therapy + usual care: $9,335	QALYs: 0.647 (0.067) WOMAC: 80.90 (57.70) OMERACT-OARSI: 37% QALYs: 0.656 (0.062) WOMAC: 73.33 (54.93) OMERACT-OARSI: 59% QALYs: 0.687 (0.064) WOMAC: 66.25 (54.57) OMERACT-OARSI: 47% QALYs: 0.663 (0.062) WOMAC: 71.74 (50.01) OMERACT-OARSI: 52%	2-1: -$191 3-1: $681 4-1: $1,579	Dominance of 2 over 1 in terms of QALYs, WOMAC, OMERACT-OARSI Cost per QALY gained 3 versus 1: $28,830 4 versus 1: $65,664 WOMAC gained 3 versus 1: $89 4 versus 1: $159 OMERACT-OARSI gained 3 versus 1: $9,710 4 versus 1: $18,275
Osteoarthritis of the knee						
Hu [84] 2012 China	CEA	WOMAC	1. Acupunture group: $69 2. Tuina manipulative therapy group: $60	WOMAC: 47.66(8.73) WOMAC: 45.83(7.65)	2-1: -$9	Cost per WOMAC gained acupuncture versus Tuina manipulative therapy: $5

*ICER: incremental cost-effectiveness ratio, †CUA: cost-utility analysis, ‡EQ-5D: European Quality of Life-5 Dimensions, §OSM: osteopathic manual therapy, ‖GP: general practitioner, ¶QALY: quality-adjusted life year, #CEA: cost-effectiveness analysis, **VAS: visual analogue scale, ††NDI: Neck Disability Index, ‡‡SMT: spinal manual therapy, §§BGA: behavioral graded activity, ‖‖PT: physiotherapy, ¶¶NPQ: Northwick Park Neck Pain Questionnaire, ##A&E: advice and exercise, ***PSWD: pulsed shortwave diathermy, †††DV: Dutch Version, ‡‡‡SF-6D: Short Form 6-Dimensions, §§§MTU: manual therapy according to the Utrecht School, ¶¶¶SF-36: Short Form 36-item Health Survey, ‖‖‖HRQoL: health-related quality of life, ###RMDQ: Roland-Morris Disability Questionnaire, ****BPM: brief pain management, ††††TAM: total active motion, ‡‡‡‡MMDT: Minnesota manual dexterity, §§§§PPT: Purdue pegboard assessment systems, ‖‖‖‖AQoL: assessment of quality of life, ¶¶¶¶LEFS: lower extremity functional scale, ####WOMAC: Western Ontario and McMaster University osteoarthritis index, *****OMERACT-OARSI: Outcomes Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International

Table 6: Results for Cost-Effectiveness and Cost-Utility Analyses.

Spinal Pain (Low Back, Upper Back, And/Or Neck)

In a randomized trial with 6 months of follow-up, Williams, et al. [42,43] assessed the cost-effectiveness of the combination of osteopathic manipulation and usual GP care compared with usual GP care alone in spinal pain. The combination of osteopathic manipulation and usual GP care was more effective in terms of the incremental QALYs gain (0.025) and also more expensive ($642 versus $457) compared with GP care alone. However, none of the incremental difference in cost or QALYs (p=0.16) were statistically significant. The combination of osteopathic manipulation and GP care was relevant to an ICER estimate of $7,471 per QALYs gained. Because this estimate is lower than the threshold of £30,000 ($63,600) (suggested by the National Institute of Clinical Excellence (NICE), this intervention may be regarded as a potentially cost-effective selection for patients with spinal pain.

Cervical spondylotic radiculopathy: In a randomized trial with 4 weeks of follow-up, Yu, et al. [44] assessed the cost-effectiveness of Tuina manipulative therapy group (rotation technique) and traction therapy group in 69 patients with cervical spondylotic radiculopathy. The Tuina manipulative therapy was dominant compared with traction therapy.

Neck pain: In a randomized trial with 12 months of follow-up, Bosmans, et al. [45-47] assessed the cost-utility and cost-effectiveness of Spinal Manipulative Therapy (SMT) compared with Behavioral Graded Activity (BGA) in 146 patients with

neck pain. BGA was more effective with statistical significance in terms of pain intensity (mean VAS score: 0.88, 95% CI: 0.02, 1.70) and disability level (mean NDI score: 2.40, 95% CI: 0.22, 4.50) compared with SMT. However, none of the differences in perceived recovery and QALYs gained between the 2 groups were significantly different (p>0.05). BGA was costlier compared with SMT, but this difference was not statistically significant (MD: -$561). BGA was possibly more cost-effective than SMT in terms of pain intensity ($623 per improved pain score) and disability ($243 per improved disability score). However, SMT was not more cost-effective compared with BGA for perceived recovery. In a randomized trial with 12 months of follow-up, Korthals-de Bos, et al. [48,49] assessed the cost-effectiveness and cost-utility of SMT, PT, and GP care in 183 patients with neck pain. SMT was significantly less expensive compared with PT (mean difference, MD: $1,837) and GP care (MD: -$2,014). Moreover, SMT was more effective than PT in improving pain intensity (MD: 1.20, 95% CI: 0.10, 2.10) significantly, but not disability (MD: 0.90, 95% CI: -1.90, 3.60). Furthermore, SMT was more effective in reducing pain compared with both PT and GP care (71.7, 62.7, 56.3, p>0.05). SMT was numerically more effective in pain intensity (MD: 0.10, 95% CI: -0.80, 1.10) and disability (MD: -1.40, 95% CI: -4.10, 1.30) compared with GP care. Moreover, SMT was numerically most effective in terms of the QALYs gain compared with PT or GP care (0.82, 0.79, 0.77). SMT was dominant over PT for pain intensity, perceived recovery, and QALYs. It was also dominant over GP care for perceived recovery and QALYs. According to range of the acceptability curve, at the ceiling cost-effectiveness ratio of zero, there was a 98% probability that manual therapy was more cost-effective than PT in terms of the intensity of pain. There were no statistically significant differences in the costs or pain intensity or disability between PT and GP care.

In a randomized trial with 6 months of follow-up, Lewis, et al. [50,51] assessed the cost-utility and cost-effectiveness of advice and exercise (A & E) plus SMT, Pulsed Shortwave Diathermy (PSWD) plus A & E, and A & E only in patients with neck pain. Compared with SMT plus A & E and PSWD plus A & E, A & E alone care was more expensive ($723 versus $587 versus $655), and more effective numerically in terms of disability (Northwick Park Neck Pain Questionnaire: 11.5 versus 10.2 versus 10.3) and QALYs (0.362 versus 0.342 versus 0.360). However, none of the MDs in cost or effect among the 3 groups were statistically significant. According to acceptability curve WTP values, A & E had a higher probability of being cost-effective (up to 60%) than SMT and PSWD (40% or less) at all of the WTP thresholds over $97. At WTP thresholds below $97, SMT had a higher probability of being cost-effective (up to 55%) than A & E and PSWD (45% or less). SMT had a higher probability of being cost-effective (up to 55%) than A & E and PSWD (30% or below) in terms of QALYs. At the WTP threshold of £30,000 ($71,700) per QALYs gained, the probabilities for SMT, A & E, and PSWD were 44%, 30%, and 26%.

In a randomized trial with 12 months of follow-up, van Dongen, et al. [52,53] assessed the cost-utility and cost-effectiveness of manual therapy by analyzing an Utrecht school group and a PT group in 181 patients with neck pain. Compared with PT, the manual therapy group was numerically less costly ($3,351 versus $3,481), more effective in terms of perceived recovery (difference: 0.09), but, less effective in terms of functional status (Neck Disability Index-Dutch Version) (continuous outcome difference: -1.03, dichotomous outcome difference: -0.01) and QALYs (difference: -0.01). Moreover, none of the MDs in cost or effect between the two groups were statistically significant. Manual therapy group was not found to be cost-effective in comparison with PT.

Musculoskeletal chest pain: In a randomized trial with 12 months of follow-up, Stochkendahl, et al. [54-56] assessed the cost-utility of a chiropractic treatment group and a self-management group in 115 patients with musculoskeletal chest pain. The chiropractic treatment group was more effective in terms of QALYs based on the EQ-5D (0.811 versus 0.802), Short Form 36-item Health Survey (SF-36) (0.765 versus 0.756), EQ-5D (0.826 versus 0.823), and SF-36 (0.788 versus 0.774) and less expensive compared with the self-management group ($4,093 versus $7,033), though the differences were not statistically significant. The chiropractic treatment group was dominant over the self-management group in terms of QALYs, EQ-5D, and the SF-36.

Low back pain: In a randomized trial with 18 months of follow-up, Critchley, et al. [57] assessed the cost-effectiveness of individual PT, spinal stabilization PT, and pain management in patients with low back pain. The pain management was dominant compared with individual PT and spinal stabilization PT. Individual PT was more expensive and statistically significantly more effective compared with spinal stabilization PT with a mean ICER estimate of $2,043 per QALYs gained. According to the entire range of acceptability curve WTP threshold the probability that individual PT was more cost-effective than spinal stabilization was below 35%. In a randomized trial with 24 months of follow-up, Niemisto, et al. [58,59] assessed the cost-effectiveness of manipulative combination treatment and GP advice in patients with low back pain. This study demonstrated reduced pain intensity for the manipulative combination treatment compared to the GP advice (VAS score: 30.7 versus 33.1, p=0.01), with statistically significance, though disability was not decreased with statistical significance (ODI score: 12.0 versus 14.0, p=0.20). According to the cost-effectiveness plane and acceptability curve using the visual analogue scale, the ICER of the manipulative combination treatment versus GP advice was acceptable 75% of the time for pain improvement. A 1-point recovery in the manipulative combination treatment compared to GP advice in VAS cost of $635. The maximum WTP threshold for the 1-point of pain improvement

was $2,603. According to the cost-effectiveness plane and acceptability curve using the ODI, the ICER for the manipulative combination treatment versus GP advice was acceptable only 65% of the time in terms of disability. The maximum WTP threshold for 1-point of disability improvement was $5,205.

In a randomized trial with 12 months of follow-up, Rivero-Arias, et al. [60,61] assessed the cost-utility of the combination of PT and advice to remain active compared with advice to remain active alone in patients with low back pain. The combination of PT and advice to remain active was more effective in number (QALY gain: 0.74 versus 0.69) and also more expensive ($512 versus $395) compared with advice to remain active alone. However, none of the incremental differences in total cost or mean QALYs (p=0.16) between the two groups was statistically significant. The combination of PT and advice to remain active was relevant to an ICER estimate of $23,807 per QALYs gained. Despite the fact that this estimation fell within the acceptability threshold of WTP ($9,677 per QALY gained), the probability that PT plus advice to remain active was a more cost-effective intervention than advice to remain active alone was calculated at only 60%. In a randomized trial with 12 months of follow-up, the UK Back Pain Exercise and Manipulation (BEAM) trial [62-64] assessed the cost-utility of GP care only, exercise plus GP care, manipulation plus GP care, and manipulation plus exercise and GP care in 1334 patients with low back pain from 14 general practices. The exercise plus GP care ($1,009), manipulation plus general GP ($1,151), and manipulation plus exercise plus GP care ($978) groups incurred higher mean total costs compared with the GP care only group ($718). The mean number of QALYs gained was also enhanced in the 3 groups (0.635, 0.659, and 0.651) compared with the GP care group (0.618). Compared with GP care, the combination of manipulation and GP care was associated with a greater mean incremental number of QALYs gained (0.041; 95% CI: 0.016-0.066) than either the combination of exercise and GP care (0.017; 95% CI: -0.017-0.051) or the manipulation plus exercise and GP care (0.033; 95% CI: -0.001-0.067). Compared with GP care, the ICURs for the manipulation plus GP care, exercise plus GP care, or manipulation plus exercise and GP care were $9,871, $17,091, and $7,861. The combination of manipulation, exercise and GP care was possibly a dominant intervention compared with exercise plus GP care due to its lower costs ($978 versus $1,009) and better clinical effects in the number of QALYs gained (0.651 versus 0.635). If the WTP was at least $20,743 per QALYs gained, according to the report conclusions, the combination of manipulation and GP care was the most cost-effective treatment.

In a randomized trial with 12 months of follow-up, Whitehurst, et al. [65,66] assessed the cost-effectiveness and cost-utility of manual PT with brief pain management (BPM) in patients with acute low back pain. Manual PT was more effective numerically in terms of disability and utility (Roland and Morris disability questionnaire mean score change: 0.33, 95% CI: -0.82-1.49, mean QALYs gained: 0.022, 95% CI: -0.02-0.07) and was also more expensive (MD: 52.19, 95% CI: -19.22-123.62) compared with GP care only. However, none of the incremental differences in cost, QALYs, or the Roland and Morris disability questionnaire between the two groups was statistically significant. Manual PT (versus BPM) was relevant to an ICER ratio estimate of $4,805 per QALYs gained. According to the cost-utility plane and acceptability curve, the ICER for manual PT versus BPM was acceptable 83% of the time given the threshold of $20,343 per QALYs gained conservatively. This report indicated an ICER of $316 per 1-point Roland and Morris disability questionnaire score improvement for manual PT versus BPM. According to the study results, manual PT was more cost-effective than BPM.

Shoulder pain: In a randomized trial with 6 months of follow-up, Bergman, et al. [67-70] assessed the cost-effectiveness of the combination of SMT plus usual GP care compared with usual GP care alone in 150 patients with shoulder pain. The combination of SMT and usual GP care was more expensive (MD: $1,208) and also more effective numerically in perceived recovery (MD: 5.0%, 95% CI: -10.1-20.2), shoulder pain (MD: 0.7, 95% CI: -1.0-2.5), and general health (MD: 0.03, 95% CI: -0.04-0.09) compared with usual GP care alone. However, none of the MDs in cost, perceived recovery, shoulder pain, and general health between the two groups were statistically significant. Only the mean shoulder disability score showed a statistically significant difference with the use of SMT plus usual GP care versus usual GP care alone (MD: 12.7, 95% CI: 1.3-24.1). The combination of SMT and usual GP care was relevant to an ICERs estimate of $241 (perceived recovery), $1,728 (shoulder pain), $96 (shoulder disability), and $40,316 (general health). At WTP threshold of $15,794 per 1-point perceived recovery improvement, the probability that SMT plus usual GP care was cost-effective was 65%.

Lateral epicondylalgia: In a randomized trial with 12 months of follow-up, Coombes, et al. [71,72] assessed the cost-utility of saline injection (0.5mL of 0.9% isotonic saline) plus GP care, saline injection plus PT and GP care, corticosteroid injection (10mg/mL of triamcinolone acetonide + 1mL of 1% lignocaine) plus GP care, and corticosteroid injection plus PT and GP care in patients with lateral epicondylalgia. The saline injection plus PT and GP care, corticosteroid injection plus GP care, and corticosteroid injection plus PT and GP care were more expensive compared with saline injection plus GP care ($844, $212, $767 versus $124), with statistical significance. The saline injection plus PT and GP care was statistically significantly more effective in terms of QALYs when compared with saline injection plus GP care (0.920 versus 0.880, p=0.032), but not when compared with for corticosteroid injection plus GP care and corticosteroid injection plus PT and GP care (0.873 versus 0.880, p=0.746; 0.891 versus 0.880, p=0.743). According to entire range of the acceptability curve WTP threshold

$35,862 values the probability of being more cost effective than saline injection plus GP care, was 81% for saline injection plus PT and GP care, 53% for corticosteroid injection plus GP care and 24% for corticosteroid injection plus PT and GP care. There is a possibility that PT was more cost effective than the alternatives.

Hand injury: In a randomized trial with 3 months of follow-up, Zhang, et al. [73] assessed the cost-effectiveness of the rehabilitation treatment group and control treatment group in 50 patients with hand injury of digital flexor tendons. The rehabilitation treatment group therapy was numerically less expensive ($1,972 versus $2,103) and more effective with statistical significance over control treatment group for functional disability (Tendon total active motion, 67.8 versus 29.3, Minnesota manual dexterity, 77 versus 55, Purdue pegboard assessment systems, 42.5 versus 31.2, $p<0.05$). The rehabilitation treatment group was dominant compared with control treatment group.

Ankle pain: In a randomized trial with 6 months of follow-up, Lin, et al. [74,75] assessed the cost-utility of combination of manual therapy and PT compared with PT only in patients with ankle fractures. The combination of manual therapy and PT was more expensive ($3,624 versus $2,804) compared with PT alone. But, none of the MDs in cost or QOL (mean AQoL score difference: 1.3, $p=0.04$), lower extremity function (mean lower extremity functional scale difference: -1.0, $p=0.70$) between two groups were statistically significantly different. Since there were no significant differences between two group in the primary outcome measures, a CEA was not managed. The authors concluded that the combination of manual therapy and PT was not a cost-effective selection compared with PT alone.

Osteoarthritis of the hip or knee: In a randomized trial with 12 months of follow-up, Pinto, et al. [40,76-78] assessed the cost-utility and the cost-effectiveness of usual care, manual therapy plus usual care, exercise therapy plus usual care, combined therapy plus usual care in 206 patients with osteoarthritis of the hip or knee. From the societal perspective, the manual therapy plus usual care was statistically less expensive compared with usual care ($7,565 versus $7,756). But none of the MDs in cost were statistically significant ($P > 0.05$). The manual therapy plus usual care, exercise therapy plus usual care and combined therapy plus usual care were more effective compared with usual care (0.656, 0.687, 0.663, 0.647) in terms of QALYs ($P < 0.05$) with statistical significance. The manual therapy plus usual care was dominant over usual care for QALYs, Western Ontario and McMaster University osteoarthritis index (WOMAC), Outcomes Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI). However, exercise therapy plus usual care had a lower probability of cost-effectiveness compared with usual care (ICER: $28,830). The probability of combined therapy plus usual care being more cost-effective compared with usual care at WTP 3GDP ($107,902) was about 50% (ICUR: $65,664). According to entire range of the acceptability curve WTP threshold $35,967 (1 GDP per capita) values, the probability that the interventions would be more cost effective than usual care was 65% for manual therapy plus usual care, 70% for exercise therapy plus usual care, and 50% for combined therapy plus usual care per additional OMERACT-OARSI responder. There is a possibility that the 3 groups were more cost-effective than the usual care.

Osteoarthritis of the knee: In a randomized trial with 4 weeks of follow-up, Hu, et al. [79] assessed the cost-effectiveness of the Tuina manipulative therapy group (revolving method plus knee flexion and extension of passive movement and active exercise) and the acupuncture group (acupuncture plus electroacupuncture) in 60 patients with osteoarthritis of the knee. The acupuncture group was more effective in terms of WOMAC (47.66 versus 45.83, $p<0.01$) with statistical significance, numerically more expensive compared with the Tuina manipulative therapy group ($69 versus $60). ICER was estimated $5 per unit of outcome improved in the acupuncture versus the Tuina manipulative therapy.

Discussion

Economic evaluations investigate the value for money of health care interventions and include Cost-Minimization Analysis (CMA), CEA, CUA, Cost-Benefit Analysis (CBA), and Cost-Consequence Analysis (CCA). CMA is used when the effect of both interventions is identical. Thus, there is no outcome measure. CEA is used when the effect of the interventions can be expressed in terms of one main outcome measurable in natural units. CUA is used when the effect of the interventions on health status has two or more important dimensions. The outcome is a utility unit which combines a quantitative and qualitative measure (QALY). CBA is used to compare interventions for two different conditions. Both costs and outcomes have to be measured in monetary terms. CCA presents the costs and consequences of numerous intercessions and the results are declared in a disconnected method and are not combined with costs [83] This study identified limited evidence suggesting that manual therapy techniques (osteopathic spinal manipulation, PT consisting of manipulation and mobilization techniques, and chiropractic manipulation), in combination with other treatments or alone, are more cost-effective than usual GP care (alone or with exercise), spinal stabilization, GP advice, advice to remain active, and BPM for improving low back pain and/or disability. Similarly, one study [67] 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 additional costs needed to achieve a 1-unit improvement in the low back or shoulder pain/disability score or 1 QALY gained were lower than the WTP thresholds reported across the studies. One study [71] also demonstrated that PT consisting of manual therapy and exercises was more cost-effective than saline and

corticosteroid injection in lateral epicondylalgia.

The chiropractic treatment group was dominant over the self-management group in musculoskeletal chest pain [54] Moreover, in osteoarthritis of hip or knee manual therapy was dominant over usual care [76] The Tuina manipulative therapy group was dominant over the traction therapy group in cervical spondylotic radiculopathy [44] The rehabilitation treatment program plus PT was dominant over medicine treatments plus guidance function training in hand injury [73] The cost-effectiveness of manual therapy compared to other treatments for improving neck pain and disability and in terms of QALYs gained was inconsistent across the studies. For example, 1 trial [48] indicated the dominance of chiropractic manipulation over PT and GP care in terms of improving neck pain and QALYs gained. In other 2 trials, BGA was more cost-effective than manual therapy, [45] and the probability of manual therapy being more cost-effective compared to A & E was too low [50] In another trial, [52] manual therapy was not found to be cost-effective in comparison with PT. Overall, the evidence regarding the cost-effectiveness of manual therapy compared with PT for reducing pain/disability related to ankle fractures [74] and with acupuncture treatment for osteoarthritis of the knee as reported in studies [79] was not sufficient or conclusive due to small sample sizes and uncertainty. It is difficult to suggest conclusions about the comparative cost-effectiveness of manual therapy treatments in patients with spinal pain because of the paucity, clinical heterogeneity, and study-related shortcomings (short follow-up, small sample, high uncertainty in the estimates of incremental cost-effectiveness ratios) of the identified evidence. For example, the use of different manual therapy techniques (manipulation, mobilization, and chiropractic care) in combination with other interventions (PT, exercise, and GP care) results in different efficacy profiles, thereby limiting the comparability of results in across studies. The limitations of the current review are as follows. The results of this review are not comparable with those of other systematic reviews [3,26-31,85-95] given the differences in the types of economic evaluation and interventions, research questions, scope, and study inclusion and exclusion criteria. The findings of these reviews were not conclusive because of the deficiency and heterogeneity of the evidence for manual therapy, [27-32] showed some extent of the cost-effectiveness of manual therapy over other treatments [3,85,89,90,92,93,94].

The applicability of the findings of the included studies may be limited to only countries with similar health care systems and utilities (calculations based on the same QOL index). In the 10 studies that manual therapy was cost-effective in the treatment of musculoskeletal diseases, when the ICERs about QALYs were converted into USD, they did not exceed the threshold of $26,963. However, there are difficulties in comparisons due to differences in treatment costs and health care system between countries. The applicability may also be limited by the differences in components of the manual therapy interventions and short follow-ups periods of the studies. Since none of the studies used a sham and a control arm, it is difficult to ascertain out the specific effects of treatment across the study treatment interventions [84] In addition, due to the nature of manual therapy, blinding of patients and care providers could not be performed. Among the studies that meet the inclusion criteria of this paper through the search, there were 2 studies for which only the abstracts were available. We sent an email to the authors of those papers, but were unable to get a reply. In addition, we found that the ICER calculated using the cost and effect data in 2 studies [66,68] did not match the ICER data presented in those studies. We sent an email to the authors about this problem, but were unable to get a reply. The strengths of the current research include the reviewer's use of comprehensive and systematic strategies to minimize the risk of bias in searching, identifying, selecting, extracting, and evaluating the initial studies. The search strategy was applied to multiple electronic databases including China and Korea and others such as references of relevant primary studies and systematic reviews. In addition, this review summarized the evidence from studies that evaluated the costs and effectiveness simultaneously through economic evaluations by providing ICERs. All of the included studies were randomized controlled trial-based economic evaluations, and this review provided a high level of evidence in judging clinical research. This study extends the review by including new studies published since the search endpoint of Tsertsvadze's report [3] as well as studies from Asian databases. Among Asian databases, Korean and Chinese database searches were conducted, but a Japanese database search was not conducted. Compared with the previous study, this research has reviewed 10 musculoskeletal diseases by adding 7 RCTs. In addition, 16 of the 18 included trials were evaluated as having a low risk of bias. Although it was concluded that only 8 of the 16 studies with low risk of bias were cost-effective, there is a difference in the number of patients per studies, and attention should be paid to interpreting the results.

This study provides a platform for further research into the cost-effectiveness of manual therapy for the treatment of musculoskeletal diseases. The findings emphasize the lack of good-quality published evidence on this issue. The insufficient evidence on cost-effectiveness may be attributed to difficulties in getting cost data, lack of expertise in economic outcomes, and/or the perceived societal inconvenience of assigning monetary units to human health [30] When the studies do not use QALYs as an outcome measure, it is difficult for decision makers to compare value for money across musculoskeletal diseases with other diseases such as respiratory disease and cancer. We recommend that future studies present unit cost calculations with costs disassembled by each service in order to enable the judgment as to whether all relevant costs for a given perspective were considered and how the total costs were calculated. If ethically valid, future trials need to include sham or

no treatment arms in order to permit the evaluation and detachment of nonspecific effects from treatment effects. Worldwide further studies including Asian countries such as China, Japan, and Korea are needed to evaluate the economic comparisons of Chuna and manual therapy for nonspecific musculoskeletal diseases.

Conclusions

We screened 3,327 economic evaluation-related references and included a total of 18 studies. In ten out of 18 studies manual therapy was cost-effective in the treatment of musculoskeletal diseases. Moreover, in five out of 10 studies manual therapy was dominant in the treatment of musculoskeletal diseases. One major limitation of this study is the absence of patient and care provider blindness and sham intervention. It is necessary to raise awareness about the importance of conducting high quality research among the manual therapy group. The benefits and detriments of the manual therapy interventions found in many of the reported disease treatments cannot be reliably concluded because of the lack of methodological quality and clinical variety of the included studies. This study provides a basis for further research into the cost-effectiveness of manual therapy in the treatment of a variety of musculoskeletal diseases. To expand the evidence base and address the complexity of this important discipline in health care, the multimodality approach should be considered. Further well-organized research including Asian databases is needed to make more definitive conclusions and effective recommendations for policy making.

References

1. Farrell JP, Jensen GM (1992) Manual therapy: a critical assessment of role in the profession of physical therapy. Phys Ther 72: 843-852.
2. DeStefano LA, Greenman PE (2010) Greenman's principles of manual medicine. 4th ed. Lippincott Williams & Wilkins 2010.
3. Tsertsvadze A, Clar C, Court R, Clarke A, Mistry H, et al. (2014) Cost-effectiveness of manual therapy for the management of musculoskeletal conditions: a systematic review and narrative synthesis of evidence from randomized controlled trials. J Manipulative Physiol Ther 37: 343-362.
4. Hoving JL, Koes BW, de Vet HC, van der Windt DA, Assendelft WJ, et al. (2002) Manual therapy, physical therapy, or continued care by a general practitioner for patients with neck pain. A randomized, controlled trial. Ann Intern Med 136: 713-722.
5. Fitzgerald GK, McClure PW, Beattie P, Riddle DL (1994) Issues in determining treatment effectiveness of manual therapy. Phys Ther 74: 227-233.
6. Jette AM, Delitto A (1997) Physical therapy treatment choices for musculoskeletal impairments. Phys Ther 77: 145-154.
7. International Federation of Orthopaedic Manipulative Therapists (IFOMT). 2012.
8. Bryans R, Decina P, Descarreaux M, Duranleau M, Marcoux H, et al. (2014) Evidence-based guidelines for the chiropractic treatment of adults with neck pain. J Manipulative Physiol Ther 37: 42-63.
9. Globe GA, Morris CE, Whalen WM, Farabaugh RJ, Hawk C (2008) Chiropractic management of low back disorders: report from a consensus process. J Manipulative Physiol Ther 31: 651-658.
10. Bryans R, Descarreaux M, Duranleau M, Marcoux H, Potter B, et al. (2011) Evidence based guidelines for the chiropractic treatment of adults with headache. J Manipulative Physiol Ther 34: 274-289.
11. Foster NE, Pincus T, Underwood MR, Vogel S, Breen A, et al. (2003) Harding G. Understanding the process of care for musculoskeletal conditions--why a biomedical approach is inadequate. Rheumatology (Oxford) 42: 401-404.
12. Girgis CM, Mokbel N, Digirolamo DJ (2014) Therapies for musculoskeletal disease: can we treat two birds with one stone? Curr Osteoporos Rep 12: 142-153.
13. Bevan S (2015) Economic impact of musculoskeletal disorders (MSDs) on work in Europe. Best Pract Res Clin Rheumatol 29: 356-373.
14. Wijnhoven HA, de Vet HC, Picavet HS (2006) Prevalence of musculoskeletal disorders is systematically higher in women than in men. Clin J Pain 22: 717-724.
15. Wijnhoven HA, de Vet HC, Picavet HS (2006) Explaining sex differences in chronic musculoskeletal pain in a general population. Pain 124: 158-166.
16. Posadzki P, Ernst E (2011) Osteopathy for musculoskeletal pain patients: a systematic review of randomized controlled trials. Clin Rheumatol 30: 285-291.
17. Picavet HS, Schouten JS (2003) Musculoskeletal pain in the Netherlands: prevalence, consequences and risk groups, the DMC (3)-study. Pain 102: 167-178.
18. Furlan AD, Yazdi F, Tsertsvadze A, Gross A, Van Tulder M, et al. (2012) 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: 953139.
19. Bronfort G, Haas M, Evans R, Leininger B, Triano J (2010) Effectiveness of manual therapies: the UK evidence report. Chiropr Osteopat 18: 3.
20. Carnes D, Mars TS, Mullinger B, Froud R, Underwood M (2010) Adverse events and manual therapy: a systematic review. Man Ther 15: 355-363.
21. Carlesso LC, Gross AR, Santaguida PL, Burnie S, Voth S, et al. (2010) Adverse events associated with the use of cervical manipulation and mobilization for the treatment of neck pain in adults: a systematic review. Man Ther 15: 434-444.
22. Kim KB, Park TY, Lee JH, Long JC, Lee SK, et al. (2008) Review on Efficacy and Safety of Manipulation Therapy including Chuna Manipulation. Journal of Korean Medicine Rehabilitation 18: 103-120.
23. Jeon YT, Park SH, Han KI, Lee JH, Ko YS (2015) Trends of Chuna Manual Therapy on Traffic Accident in Korea from 2005 to 2014. Journal of Korean Medicine Rehabilitation 25: 89-96.
24. Kumar S, Beaton K, Hughes T (2013) The effectiveness of massage therapy for the treatment of nonspecific low back pain: a systematic review of systematic reviews. Int J Gen Med 6: 733-741.

25. Zhang Y, Chen P, Ke JL (2010) Treating lumbar spinal stenosis using tuina and fumigating and washing: report of 112 cases. J Tradit Chin Med Zhejiang 2010: 838-839.

26. Maund E, Craig D, Suekarran S, Neilson A, Wright K, et al. (2012) Management of frozen shoulder: a systematic review and cost-effectiveness analysis. Health Technol Assess 16: 1-264.

27. Indrakanti SS, Weber MH, Takemoto SK, Hu SS, Polly D, et al. (2012) Value-based care in the management of spinal disorders: a systematic review of cost-utility analysis. Clin Orthop Relat Res 470: 1106-1123.

28. Driessen MT, Lin CW, van Tulder MW (2012) Cost-effectiveness of conservative treatments for neck pain: a systematic review on economic evaluations. Eur Spine J 21: 1441-1450.

29. Furlan AD, Yazdi F, Tsertsvadze A (2010) 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.

30. Dagenais S, Roffey DM, Wai EK, Haldeman S, Caro J (2009) Can cost utility evaluations inform decision making about interventions for low back pain? Spine J 9: 944-957.

31. Brown A, Angus D, Chen S, et al. (2005) Costs and outcomes of chiropractic treatment for low back pain. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 56.

32. Stevans JM, Zodet MW (2012) 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 35: 589-599.

33. Grieves B, Menke JM, Pursel KJ (2009) Cost minimization analysis of low back pain claims data for chiropractic vs medicine in a managed care organization. J Manipulative Physiol Ther 32: 734-739.

34. Haas M, Sharma R, Stano M (2005) Cost-effectiveness of medical and chiropractic care for acute and chronic low back pain. J Manipulative Physiol Ther 28: 555-563.

35. Driessen MT, Lin CW, van Tulder MW (2012) Cost-effectiveness of conservative treatments for neck pain: a systematic review on economic evaluations. Eur Spine J 21: 1441-1450.

36. Korean Society of Chuna Manual Medicine for Spine & Nerves. Chuna manual medicine. 2nd ed. Korean Society of Chuna Manual Medicine for Spine & Nerves 2014: 6-14.

37. Tang S, Qian X, Zhang Y, Liu Y (2016) Treating low back pain resulted from lumbar degenerative instability using Chinese Tuina combined with core stability exercises: A randomized controlled trial. Complement Ther Med 25: 45-50.

38. Kim CG, Mun SJ, Kim KN, Shin BC, Kim NK, et al. (2016) Economic evaluation of manual therapy for musculoskeletal diseases: a protocol for a systematic review and narrative synthesis of evidence. BMJ open 6: 010556.

39. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339: 2535.

40. Abbott JH, Robertson MC, McKenzie JE, Baxter GD, Theis JC, et al. (2009) Exercise therapy, manual therapy, or both, for osteoarthritis of the hip or knee: a factorial randomised controlled trial protocol. Trials 10: 11.

41. Korthals-de Bos I, van Tulder M, van Dieten H, Bouter L (2004) Economic evaluations and randomized trials in spinal disorders: principles and methods. Spine (Phila Pa 1976) 15: 442-448.

42. Williams NH, Edwards RT, Linck P, Muntz R, Hibbs R, et al. (2004) Cost-utility analysis of osteopathy in primary care: results from a pragmatic randomized controlled trial. Fam Pract 21: 643-650.

43. Williams NH, Wilkinson C, Russell I, Edwards RT, Hibbs R, et al. (2003) Randomized Osteopathic Manipulation Study (ROMANS): pragmatic trial for spinal pain in primary care. Fam Pract 20: 662-669.

44. Yu Jia, Xie Yanming, Zhu Liguo, Yu Jie, Zhang Qing (2008) Cost-effectiveness analysis of rotating manipulation therapy for cervical spondylotic radiculopathy. Chinese Journal of Information on Traditional Chinese Medicine 15: 7-8.

45. Bosmans JE, Pool JJM, de Vet HCW, van Tulder MW, Ostelo RW (2011) 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 36: 1179-1186.

46. Pool JJ, Ostelo RW, Koke AJ, Bouter LM, de Vet HC (2006) 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 11: 297-305.

47. Pool JJ, Ostelo RW, Knol DL, Vlaeyen JW, Bouter LM, et al. (2010) Is a behavioral graded activity program more effective than manual therapy in patients with subacute neck pain? Results of a randomized clinical trial. Spine 35: 1017-1024.

48. Korthals-de Bos IBC, Hoving JL, van Tulder MW, Rutten-van Mölken MP, Adèr HJ, et al. (2003) Cost effectiveness of physiotherapy, manual therapy, and general practitioner care for neck pain: economic evaluation alongside a randomised controlled trial. BMJ 326: 911.

49. Hoving JL, Koes BW, de Vet HC, van der Windt DA, Assendelft WJ, et al. (2002) Manual therapy, physical therapy, or continued care by a general practitioner for patients with neck pain. A randomized, controlled trial. Ann Intern Med 136: 713-722.

50. Lewis M, James M, Stokes E, et al. (2007) An economic evaluation of three physiotherapy treatments for non-specific neck disorders alongside a randomized trial. Rheumatology 46: 1701-1708.

51. Dziedzic K, Hill J, Lewis M, Sim J, Daniels J, et al. (2005) 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 53: 214-222.

52. van Dongen JM, Groeneweg R, Rubinstein SM, Bosmans JE, Oostendorp RA, et al. (2016) Cost-effectiveness of manual therapy versus physiotherapy in patients with sub-acute and chronic neck pain: a randomised controlled trial. Eur Spine J 25: 2087-2096.

53. Groeneweg R, Kropman H, Leopold H, van Assen L, Mulder J, et al. (2010) The effectiveness and cost-evaluation of manual therapy and physical therapy in patients with sub-acute and chronic nonspecific neck pain. Rationale and design of a Randomized Controlled Trial (RCT). BMC Musculoskelet Disord 11:14.

54. Stochkendahl MJ, Sørensen J, Vach W, Christensen HW, Høilund-Carlsen PF, et al. (2016) Cost-effectiveness of chiropractic care versus self-management in patients with musculoskeletal chest pain. Open

Heart 3: 000334.

55. Stochkendahl MJ, Christensen HW, Vach W, Høilund-Carlsen PF, Haghfelt T, et al. (2012) Chiropractic treatment vs self-management in patients with acute chest pain: a randomized controlled trial of patients without acute coronary syndrome. J Manipulative Physiol Ther 35: 7-17.

56. Stochkendahl MJ, Christensen HW, Vach W, Høilund-Carlsen PF, Haghfelt T, et al. (2012) A randomized clinical trial of chiropractic treatment and self-management in patients with acute musculoskeletal chest pain: 1-year follow-up. J Manipulative Physiol Ther 35: 254-262.

57. Critchley DJ, Ratcliffe J, Noonan S, Jones RH, Hurley MV (2007) 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) 32: 1474-1481.

58. Niemisto L, Rissanen P, Sarna S, Lahtinen-Suopanki T, Lindgren KA, et al. (2005) 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 30: 1109-1115.

59. Niemisto L, Lahtinen-Suopanki T, Rissanen P, Lindgren KA, Sarna S, et al. (2003) A randomized trial of combined manipulation, stabilizing exercises, and physician consultation compared to physician consultation alone for chronic low back pain. Spine 28: 2185-2191.

60. Rivero-Arias O, Gray A, Frost H, Lamb SE, Stewart-Brown S (2006) Cost-utility analysis of physiotherapy treatment compared with physiotherapy advice in low back pain. Spine (Phila Pa 1976) 31: 1381-1387.

61. Frost H, Lamb SE, Doll HA, Carver PT, Stewart-Brown S (2004) Randomised controlled trial of physiotherapy compared with advice for low back pain. BMJ 329: 708.

62. UK BEAM Trial Team (2004) United Kingdom Back Pain Exercise and Manipulation (UK BEAM) randomised trial: cost effectiveness of physical treatments for back pain in primary care. BMJ 329: 1381.

63. Brealey S, Burton K, Coulton S, Farrin A, Garratt A, et al. (2003) 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 3: 16.

64. UK BEAM Trial Team (2004) United Kingdom Back Pain Exercise and Manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ 329: 1377.

65. Whitehurst DG, Lewis M, Yao GL, Bryan S, Raftery JP, et al. (2007) 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 57: 466-473.

66. Hay EM, Mullis R, Lewis M, et al. (2005) Comparison of physical treatments versus a brief pain-management programme for back pain in primary care: a randomised clinical trial in physiotherapy practice. Lancet 365: 2024-2030.

67. Bergman GJ, Winter JC, van Tulder MW, Meyboom-de JB, Postema K, et al. (2010) 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 11: 200.

68. Bergman GJD, Winters JC, van der Heijden GJMG, Postema K, Meyboom-de Jong B (2002) 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 25: 543-549.

69. Bergman GJD, Winters JC, Groenier KH, Pool JJ, Meyboom-de Jong B, et al. (2004) Manipulative therapy in addition to usual medical care for patients with shoulder dysfunction and pain: a randomized, controlled trial. Ann Intern Med 141: 432-439.

70. Bergman GJ, Winters JC, Groenier KH, Meyboom-de JB, Postema K, et al. (2010) 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 33: 96-101.

71. Coombes BK, Connelly L, Bisset L, Vicenzino B (2016) Economic evaluation favours physiotherapy but not corticosteroid injection as a first-line intervention for chronic lateral epicondylalgia: evidence from a randomised clinical trial. Br J Sports Med 50: 1400-1405.

72. Coombes BK, Bisset L, Connelly LB, Brooks P, Vicenzino B (2009) Optimising corticosteroid injection for lateral epicondylalgia with the addition of physiotherapy: a protocol for a randomised control trial with placebo comparison. BMC Musculoskelet Disord 10: 76.

73. Zhang Xin, Wu Hong, Ran Chunfeng, et al. (2009) The cost-effectiveness analysis of rehabilitation on hand injury patients. Chinese Journal of Rehabilitation Medicine 24: 33-36.

74. Lin CW, Moseley AM, Haas M, Refshauge KM, Herbert RD (2008) Manual therapy in addition to physiotherapy does not improve clinical or economic outcomes after ankle fracture. J Rehabil Med 40: 433-439.

75. Lin CC, Moseley AM, Refshauge KM, Haas M, Herbert RD (2006) Effectiveness of joint mobilisation after cast immobilisation for ankle fracture: a protocol for a randomised controlled trial [ACTRN012605000143628]. BMC Musculoskelet Disord 7: 46.

76. Pinto D, Robertson MC, Abbott JH, Hansen P, Campbell AJ, et al. (2013) Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee. 2: economic evaluation alongside a randomized controlled trial. Osteoarthritis Cartilage 21: 1504-1513.

77. Abbott JH, Robertson MC, Chapple C, Pinto D, Wright AA, et al. (2013) Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness. Osteoarthritis Cartilage 21: 525-34.

78. Pinto D, Robertson MC, Hansen P, Abbott JH, MOA Trial Team (2011) Economic evaluation within a factorial-design randomised controlled trial of exercise, manual therapy, or both interventions for osteoarthritis of the hip or knee: study protocol. BMJ Open 1: 000136.

79. Hu Wei-min, Dong Gui-rong (2012) Cost effectiveness of acupuncture and moxibustion in treatment of knee osteoarthritis. Chinese Community Doctors 14: 224-226.

80. Furlan AD, Pennick V, Bombardier C, van Tulder M (2009) 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 34: 1929-1941.

81. Balk EM, Bonis PA, Moskowitz H, Schmid CH, Ioannidis JP, et al.

(2002) Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. JAMA 287: 2973-2982.

82. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, et al. (1998) Does quality of reports of randomized trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 352: 609-613.

83. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL (2005) Methods for the economic evaluation of health care programmes. 3rd ed. USA: Oxford University Press 2005.

84. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, et al. (2013) Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. Int J Nurs Stud 50: 587-592.

85. Canter PH, Coon JT, Ernst E (2006) Cost-effectiveness of complementary therapies in the United Kingdom—a systematic review. Evid Based Complement Altern Med 3: 425-432.

86. Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG (2003) A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. Ann Intern Med 138: 898-906.

87. Coon JT, Ernst E (2005) A systematic review of the economic evaluation of complementary and alternative medicine. Perfusion 18: 202-214.

88. Herman PM, Craig BM, Caspi O (2005) Is complementary and alternative medicine (CAM) cost-effective? A systematic review. BMC Altern Med 5: 11.

89. Lin CWC, Haas M, Maher CG, Machado LAC, van Tulder MW (2011) Cost-effectiveness of general practice care for low back pain: a systematic review. Eur Spine J 20: 1012-1023.

90. Lin CWC, Haas M, Maher CG, Machado LAC, van Tulder MW (2011) Cost-effectiveness of guideline-endorsed treatments for low back pain: a systematic review. Eur Spine J 20: 1024-1038.

91. Van Der Roer N, Goossens MEJB, Evers SMAA, van Tulder MW (2005) What is the most cost-effective treatment for patients with low back pain? A systematic review. Best Pract Res Clin Rheumatol 19: 671-684.

92. White AR, Ernst E (2000) Economic analysis of complementary medicine: a systematic review. Complement Ther Med 8: 111-118.

93. Herman PM, Poindexter BL, Witt CM, Eisenberg DM (2012) Are complementary therapies and integrative care cost-effective? A systematic review of economic evaluations. BMJ Open 2: 001046.

94. Lewis R, Williams N, Matar HE, Din N, Fitzsimmons D, et al. (2011) The clinical effectiveness and cost-effectiveness of management strategies for sciatica: systematic review and economic model. Health Technol Assess 15: 1-578.

95. Michaleff ZA, Lin CW, Maher CG, van Tulder MW (2012) Spinal manipulation epidemiology: systematic review of cost effectiveness studies. J Electromyogr Kinesiol 22: 655-662.