

Manuscript Number:

Title: Osteopathic manipulative treatment: A systematic review and critical appraisal of comparative effectiveness and health economics research

Article Type: Systematic Review

Keywords: osteopathy, osteopathic manipulative treatment, comparative effectiveness research, economic evaluation, pragmatic research

Corresponding Author: Dr. Amie Steel, PhD

Corresponding Author's Institution: Endeavour College of Natural Health

First Author: Amie Steel, PhD

Order of Authors: Amie Steel, PhD; Tobias Sundberg; Rebecca Reid; Lesley Ward; Felicity Bishop; Matthew Leach; Holger Cramer; Jon Wardle; Jon Adams

Abstract: Background: In recent years, evidence has emerged regarding the effectiveness of osteopathic manipulative treatments (OMT). Despite growing evidence in this field, there is need for appropriate research designs that effectively reflect the person-centred system of care promoted in osteopathy and provide data which can inform policy decisions within the healthcare system.

Objective: Identify, appraise and synthesise the evidence from comparative effectiveness and economic evaluation research involving OMT. Design: Systematic literature review.

Methods: A database search was conducted using CINAHL, PubMed, PEDro, AMED, SCOPUS and OSTMED.DR, from their inception to May 2015. Two separate searches were undertaken to identify original research articles encompassing the economic evaluation and comparative effectiveness of OMT. Identified comparative effectiveness studies were evaluated using the Cochrane risk of bias tool and appraised using the Good Reporting of Comparative Effectiveness (GRACE) principles. Identified economic studies were assessed with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.

Results: Sixteen studies reporting the findings of comparative effectiveness (n=9) and economic evaluation (n=7) research were included. The comparative effectiveness studies reported outcomes for varied health conditions and the majority (n=6) demonstrated a high risk of bias. The economic evaluations included a range of analyses and considerable differences in the quality of reporting were evident.

Conclusion: Despite some positive findings, published comparative effectiveness and health economic studies in OMT are of insufficient quality and quantity to inform policy and practice. High quality, well-designed, research that aligns with international best practice is greatly needed to build a pragmatic evidence base for OMT.

21 June 2016

Dear Dr Ann Moore,

Please find attached the article '**Osteopathic manipulative treatment: A systematic review and critical appraisal of comparative effectiveness and health economics research**', for exclusive consideration for publication in the *Manual Therapy* Journal.

This manuscript presents the first review of the comparative effectiveness and cost effectiveness research in osteopathic manipulative treatment. The review offers a critical appraisal of existing research and provides recommendations to strengthen future research in this important field.

All the authors have made substantial contributions to this manuscript. Drs Amie Steel and Tobias Sundberg conceptualised the study and, in collaboration with Ms Rebecca Reid, developed the overall protocol for the review. Ms Reid undertook the search for manuscripts in line with the developed protocol and Dr Sundberg extracted the data from included papers with sample verification of both stages by Dr Steel. Drs Lesley Ward and Felicity Bishop were responsible for the Risk of Bias assessments and Dr Ward collaborated with Dr Holger Cramer to complete the appraisal of included papers according to the GRACE guidelines. Assessment of papers to determine their alignment with comparative effectiveness principles in line with the PRECIS-2 tool was undertaken by Drs Steel and Sundberg. Evaluation of health economic research manuscripts in accordance with the CHEERS statement was completed by Dr Steel and Dr Jon Wardle. Dr Matthew Leach contributed substantially to the interpretation of findings and recommendations for future research. All authors contributed to the drafting, editing and finalisation of the submitted manuscript.

We feel that the significance of our findings will be of particular interest to the international audience of your journal.

Yours sincerely,

A handwritten signature in dark ink, appearing to read 'Amie Steel', is centered within a light yellow rectangular box.

Amie Steel

Australian Research Center in Complementary and Integrative Medicine

Faculty of Health

University of Technology, Sydney

Osteopathic manipulative treatment: A systematic review and critical appraisal of comparative effectiveness and health economics research

Amie Steel^{1,2}, Tobias Sundberg^{1,3}, Rebecca Reid², Lesley Ward^{1,4}, Felicity L Bishop^{1,5},
Matthew Leach^{1,6}, Holger Cramer^{1,7}, Jon Wardle¹, Jon Adams¹

¹Australian Research Centre in Complementary and Integrative Medicine, Faculty of Health,
University of Technology Sydney, 15 Broadway, Ultimo NSW 2007, Australia

²Endeavour College of Natural Health, Level 2, 269 Wickham St Fortitude Valley QLD 4006,
Australia

³Research Unit for Studies of Integrative Health Care, Karolinska Institutet (NVS/OMV),
Alfred Nobels Alle 23, 141 83 Stockholm, Sweden

⁴Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences
(NDORMS), B4495, Oxford OX3 7LD, University of Oxford, Oxford, United Kingdom

⁵Centre for Applications of Health Psychology, Faculty of Social Human and Mathematical
Sciences, Building 44 Highfield Campus, University of Southampton, Southampton, SO17
1BJ, United Kingdom

⁶School of Nursing & Midwifery, Health Economics & Social Policy Group, University of
South Australia, 101 Currie St, Adelaide, Australia

⁷Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of Medicine,
University of Duisburg-Essen, 45141 Duisburg, Germany

Corresponding Author

Dr Amie Steel

Email: amie.steel@uts.edu.au

Phone: +61 7 3253 9523

Endeavour College of Natural Health

Level 2, 269 Wickham St

Fortitude Valley QLD 4006

Australia

Osteopathic manipulative treatment: A systematic review and critical appraisal of comparative effectiveness and health economics research

ABSTRACT

Background: In recent years, evidence has emerged regarding the effectiveness of osteopathic manipulative treatments (OMT). Despite growing evidence in this field, there is need for appropriate research designs that effectively reflect the person-centred system of care promoted in osteopathy and provide data which can inform policy decisions within the healthcare system.

Objective: Identify, appraise and synthesise the evidence from comparative effectiveness and economic evaluation research involving OMT.

Design: Systematic literature review.

Methods: A database search was conducted using CINAHL, PubMed, PEDro, AMED, SCOPUS and OSTMED.DR, from their inception to May 2015. Two separate searches were undertaken to identify original research articles encompassing the economic evaluation and comparative effectiveness of OMT. Identified comparative effectiveness studies were evaluated using the Cochrane risk of bias tool and appraised using the Good Reporting of Comparative Effectiveness (GRACE) principles. Identified economic studies were assessed with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.

Results: Sixteen studies reporting the findings of comparative effectiveness (n=9) and economic evaluation (n=7) research were included. The comparative effectiveness studies reported outcomes for varied health conditions and the majority (n=6) demonstrated a high risk of bias. The economic evaluations included a range of analyses and considerable differences in the quality of reporting were evident.

1 Conclusion: Despite some positive findings, published comparative effectiveness and
2 health economic studies in OMT are of insufficient quality and quantity to inform policy and
3 practice. High quality, well-designed, research that aligns with international best practice is
4 greatly needed to build a pragmatic evidence base for OMT.
5
6
7
8
9

10 Keywords: osteopathy, osteopathic manipulative treatment, comparative effectiveness
11 research, economic evaluation, pragmatic research
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Osteopathic manipulative treatment: A systematic review and critical appraisal of comparative effectiveness and health economics research

ABSTRACT

Background: In recent years, evidence has emerged regarding the effectiveness of osteopathic manipulative treatments (OMT). Despite growing evidence in this field, there is need for appropriate research designs that effectively reflect the person-centred system of care promoted in osteopathy and provide data which can inform policy decisions within the healthcare system.

Objective: Identify, appraise and synthesise the evidence from comparative effectiveness and economic evaluation research involving OMT.

Design: Systematic literature review.

Methods: A database search was conducted using CINAHL, PubMed, PEDro, AMED, SCOPUS and OSTMED.DR, from their inception to May 2015. Two separate searches were undertaken to identify original research articles encompassing the economic evaluation and comparative effectiveness of OMT. Identified comparative effectiveness studies were evaluated using the Cochrane risk of bias tool and appraised using the Good Reporting of Comparative Effectiveness (GRACE) principles. Identified economic studies were assessed with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.

Results: Sixteen studies reporting the findings of comparative effectiveness (n=9) and economic evaluation (n=7) research were included. The comparative effectiveness studies reported outcomes for varied health conditions and the majority (n=6) demonstrated a high risk of bias. The economic evaluations included a range of analyses and considerable differences in the quality of reporting were evident.

1 Conclusion: Despite some positive findings, published comparative effectiveness and
2 health economic studies in OMT are of insufficient quality and quantity to inform policy and
3 practice. High quality, well-designed, research that aligns with international best practice is
4 greatly needed to build a pragmatic evidence base for OMT.
5
6
7
8
9

10 Keywords: osteopathy, osteopathic manipulative treatment, comparative effectiveness
11 research, economic evaluation, pragmatic research
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

INTRODUCTION

Osteopathic healthcare is a holistic person-centred system of care aligned with the philosophy, principles of practice and application of osteopathic manipulative treatment (OMT) (1). While OMT can be prescribed for the management of various health conditions, it is most commonly indicated for the care of painful disorders such as low back pain (2), headaches (3), and neck pain (4). In addition to OMT, osteopathic practitioners may also prescribe other medical therapies (including pharmaceuticals) depending on the medico-legal and regulatory standards of the country and scope of osteopathic training and practice (1, 5). Osteopathic healthcare has diverse representation across health systems internationally, ranging from full integration within conventional health care systems (i.e. in the US), through to semi-integration as allied and complementary health care therapists (i.e. in many European and Australasian countries) (1). Nonetheless, the primary shared component of all streams of osteopathic practice is OMT applied with an understanding of the relationship between the structure and function of the human body (1).

The prevalence of osteopathic healthcare use has been reported at less than 5% of the general population in Australia (6) and as high as 16% in the United States (7). However, higher rates of use in Australia are found amongst specific populations such as the middle-aged (16%) (8) and pregnant women (6.2%) (9). The use of osteopathic services is also much higher amongst individuals with specific health conditions, for example 13.4% of UK adults with back pain (10). This suggests that there is modest demand for osteopathic healthcare services, at least in Western countries.

Research investigating the effectiveness of osteopathic treatments has intensified over the past decade. Current evidence from randomised controlled trials (RCTs) and systematic reviews of RCTs suggests that osteopathy-related interventions are effective in improving outcomes in patients with back pain (11), neck pain (12), sciatica (13), chronic obstructive pulmonary disease (14), irritable bowel syndrome (15, 16) and various paediatric conditions (17). While the RCT design is considered the gold standard for demonstrating efficacy (18),

1 concerns have been raised regarding the applicability of the explanatory RCT to everyday
2 clinical practice (REF). These concerns have led to the promotion of comparative
3 effectiveness research (CER) - a pragmatic research design generating evidence that can
4 be more efficiently translated into patient care and health policy (19). CER is defined as “*the*
5 *generation and synthesis of evidence that compares the benefits and harms of alternative*
6 *methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the*
7 *delivery of care*” (20). Suggested key elements of CER include (a) direct comparisons of
8 active treatments; (b) study patients, clinicians and interventions that are representative of
9 usual practice; and (c) a focus on helping patients, clinicians and policy makers to make
10 informed choices (21). While CER has been used to investigate OMT (22, 23), such studies
11 have not yet been subject to systematic review that specifically focusses on OMT, and so
12 the contribution of CER to the evidence-base in osteopathy is yet to be established.

13 CER focuses not only on whether an intervention makes an impact under “real-world”
14 conditions, but also on whether an intervention is beneficial in relation to the resources it
15 consumes (18). This latter feature fits within the broad field of health economics through
16 which policy makers attempt to manage the rise of health care expenditure by prioritizing
17 between competing health care interventions based on value for money (24). Accordingly,
18 health economic evaluations are crucial elements in political decision-making regarding the
19 reimbursement and funding of health services (24). Economic evaluation of health
20 interventions, such as osteopathic care, can be undertaken based either on clinical trial data
21 or the modelling of data from a range of data sources (24). Whilst there have been some
22 attempts to understand the cost-effectiveness of health services encompassing osteopathic
23 healthcare, such as spinal manipulation (25) or manual therapy more generally (26), the
24 findings of these studies have not yet provided firm conclusions regarding the cost
25 effectiveness of osteopathic care as a discrete treatment option. Furthermore, cost-
26 effectiveness studies in OMT have not previously been reviewed in relation to CER, despite
27 the natural synergies between these approaches.

1 With this in mind, this paper presents the first critical systematic review of comparative
2 effectiveness research and health economic evaluations of OMT. The aim was to review and
3 critically appraise comparative effectiveness and health economic research on OMT. The
4 objectives were to elucidate the contribution that these research approaches can make to
5 the OMT evidence-base, to identify strengths and limitations of existing studies, and to make
6 recommendations for improving future studies using CER and health economic approaches.
7
8
9
10
11
12
13

14 MATERIALS AND METHODS

15
16 A comprehensive search of the literature was undertaken to identify published original
17 research examining the comparative-effectiveness and health economics of OMT. Standard
18 systematic review techniques were followed in accordance with the PRISMA statement (27)
19
20
21
22
23

24 Search strategy

25
26 An initial search was conducted of the following databases, from their inception to May 2015:
27 CINAHL, PubMed, PEDro, AMED, SCOPUS and OSTMED.DR. Two distinct searches were
28 undertaken in each database; one focusing on the economic evaluation of OMT, and the
29 other on the comparative effectiveness of OMT. Shared search terms for both searches
30 included *osteopath**, *random**, *clinical trial*, *manipul**, *manual therapy*, and *manual medicine*.
31 The term *comparative effectiveness* was applied to the search for research articles
32 examining the comparative effectiveness of OMT. Likewise, *cost** was used to identify
33 papers exploring health economics. To ensure a broad range of articles were identified,
34 manual searching was also conducted by reviewing references from existing review articles
35 located through the database search in September 2015.
36
37
38
39
40
41
42
43
44
45
46
47
48

49 Inclusion and exclusion criteria

50
51 Articles were excluded if they did not present original empirical data, were not written in
52 English, and did not examine OMT as a system of care. Articles were included if they
53 evaluated health economic outcomes of OMT or compared the effectiveness of OMT with
54 another available treatment or technique or standard care (including 'no care' where relevant
55
56
57
58
59
60
61
62
63
64
65

to the condition). No limits were placed on date of publication. Articles were screened, short-listed and selected for data extraction by R.R. with sample verification of identified references undertaken by A.S. throughout the screening process. Any disagreements were resolved by discussion until consensus was reached. The full literature search processes for comparative effectiveness and health economic studies are outlined in Figures 1 and 2 respectively.

Data extraction

Data were extracted by one investigator (T.S.) and verification of extracted data undertaken by another investigator (A.S.). Discussion was used to reach consensus in case of any disagreements. Data were extracted in accordance with the template provided by the Cochrane handbook guidelines (28) and modified for the purposes of this review to include information on methods, participants, intervention and outcomes.

Critical analysis

Risk of Bias

Comparative effectiveness articles were independently evaluated for risk of bias by two investigators (L.W., F.B.) using criteria outlined in the Cochrane Handbook for Systematic Reviews (29). The Cochrane risk of bias tool was used to assess the domains of selection bias (random sequence generation, allocation concealment), performance bias (blinding of personnel and participants), detection bias (blinding of outcome assessment), attrition bias (drop-outs), reporting bias (selective reporting of outcomes), and any other sources of bias as identified by the reviewers. Ratings were compared (73% agreement, kappa = 0.60) and differences were resolved through discussion in order to reach consensus.

Appraisal of comparative effectiveness studies

Articles reporting comparative effectiveness research were scored using the PRagmatic-Explanatory Continuum Indicator Summary-2 (PRECIS-2) tool (30) and independently categorised as employing either an explanatory or observational design by two investigators

(A.S., T.S.). All papers identified through PRECIS-2 categorisation as reporting observational studies were assessed in accordance with the Good Research for Comparative Effectiveness (GRACE) principles (H.C., L.W) (31).

Appraisal of health economic studies

The quality of included health economics articles was assessed in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (32). The CHEERS statement is intended to optimise reporting guidance for economic evaluations via a checklist that is subdivided into six main categories: (1) title and abstract; (2) introduction; (3) methods; (4) results; (5) discussion; and (6) other. The checklist consists of 24 items, however one item was excluded from our analysis (i.e. item 12: “measurement and valuation of preference based outcomes”) as the item is optional and was not applicable to any of the included studies. Each paper was compared against the CHEERS checklist by two authors (A.S., J.W.) and awarded a score out of 23. Any differences between rater scores were discussed and a consensus decision made.

Data analysis

Given the nature and broad scope of the review, findings were summarised in narrative form.

RESULTS

The outcomes of the literature search for health economics analyses (n=8) (33-40) and comparative effectiveness research (n=8) (41-48) of OMT are presented in Figures 1 and 2, respectively. A total of 16 papers reported on the findings of 15 studies, with one study reporting two smaller yet distinct analyses (39, 40). Research from North America dominated the included studies with 10 papers originating from the United States (35-38, 42, 44-48) and one from Canada (41). Studies originating from the United Kingdom (33, 39, 40, 43) and Italy (34) made up the remaining five papers. The majority of included studies (n=12)

1 sampled adult participants, with a quarter (n=4) involving children. Sample sizes varied
2 substantially between studies, from 29 (41) to 1556 (35) participants (mean = 276; median
3 =90). However, when retrospective clinical audits (n=2) were excluded, the sample size
4 range narrowed considerably (i.e. 29 to 178 participants; mean = 89; median = 58).
5
6 Headache (38, 41), neck (39, 40, 47) and back pain (35, 39, 40, 42, 43, 46) were the most
7 common conditions examined in the included studies; other conditions included otitis media
8 (48), spastic cerebral palsy (44, 45), pancreatitis (37) and preterm birth (34). Studies were
9 undertaken in either community clinics (39-46, 48) or hospital environments (34-38, 47, 49).
10
11 Results of the selected studies are displayed in Table 1.
12
13
14
15
16
17
18
19
20

21 Comparative effectiveness research

22
23 The comparative effectiveness studies (n=8) identified in this review included both adult and
24 paediatric populations. The characteristics of the interventions used in these studies were
25 either OMT with manipulation or OMT in combination with another intervention (i.e.
26 progressive muscle relaxation, or herbal medicine). OMT was compared with standard care
27 in five studies (42, 44-47), sham OMT in two studies (46, 48), acupuncture (44, 45) in two
28 studies, and pharmaceuticals (47) and physiotherapy (43) in one study each. Where studies
29 included sham OMT, at least one arm of the study included access to standard care or a
30 comparative treatment intervention. Some studies described participants as accessing no
31 care or a wait-list control but the studies specified participants to continue accessing usual
32 care through the study period (46) and as such these studies were considered as using
33 'standard care' as the comparator.
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 *Outcomes of comparative effectiveness research*

49
50 In line with the heterogeneous characteristics of the identified studies, the reported
51 outcomes of OMT were also mixed. Research examining the effectiveness of OMT for the
52 management of low back pain found no significant difference in benefit when compared with
53 standard allopathic treatment (42), group exercise or physiotherapy (43), or sham
54 manipulation (46). The outcomes of ketorolac injection for acute neck pain was comparable
55
56
57
58
59
60
61
62
63
64
65

1 to OMT in a study conducted in an emergency department, whereby both groups reported a
2 similarly significant reduction in pain intensity (47). Significant improvement in mobility
3 measures were reported for OMT treatment of spastic cerebral palsy when compared with
4 wait-list control or acupuncture (45). Similarly, OMT treatment was found to reduce the
5 occurrence of headache-free days for individuals experiencing tension headaches, but with
6 no statistically significant difference in the intensity of the headaches, when compared with
7 progressive muscle relaxation exercises (41).

16 *Critical appraisal of comparative effectiveness research*

18 The majority of the eight studies identified as comparative effectiveness studies of OMT
19 were assessed as having a high risk of bias for blinding of participants (6 studies, 75%) and
20 blinding of outcome assessment (4 studies, 50%), and unclear risk of bias for selective
21 outcome reporting (6 studies, 75%) and allocation concealment (5 studies, 63%). The only
22 domain with an overall low risk of bias across the eight studies was random sequence
23 generation (6 studies, 75%). The two studies with the lowest overall risk of bias were
24 characterised as having robust randomisation, well-reported allocation concealment, blinded
25 outcome assessors, and low rates of attrition (45, 48). The study with the lowest risk of bias
26 was undertaken by Wahl et al (48). The risk of bias assessment for all studies is reported in
27 Table 2.

41 According to the PRECIS-2 scores (presented in Table 2), all comparative effectiveness
42 studies were identified as 'observational' rather than 'explanatory' research. McReynolds et
43 al (47) and Andersson et al (42) most closely fit the criteria for an 'observational'
44 comparative effectiveness study while Liccardone (46) most closely aligned with the
45 characteristics of an explanatory randomised-control trial study design. The study design
46 element which most consistently supported pragmatic comparative effectiveness research
47 was the setting of the included studies as they were all conducted in a real-life clinical
48 environment. The factors that detracted from these studies aligning with real-life clinical
49 practice to the degree required for pragmatic clinical research included the lack of flexibility

1 in the delivery of osteopathic treatments and the requirement that clinicians adhere to a
2 structured treatment protocol (results not shown).
3

4
5 Compliance with the GRACE statement checklist differed across all studies (see Table 3).
6

7 Three studies (42, 46, 47) complied with 10 of the 12 checklist items and one study complied
8 with 9 of the 12 checklist items. The lowest attributed score was for the study by Wahl et al
9 (48), which complied with 3 of the 12 items. All studies were non-compliant with two items of
10 the GRACE checklist: details of treatment were not adequately recorded; and meaningful
11 analyses were not conducted to test key assumptions on which the primary results were
12 based. Other common areas of non-compliance included failing to restrict the study
13 population to new initiators of treatment, and overlooking important covariates or
14 confounding variables in the study design or analysis.
15
16
17
18
19
20
21
22
23
24

25 Economic analysis research

26 *Study characteristics*

27
28 The included economic papers (n=8) represented a range of economic analyses, including
29 costing studies (33, 35, 38, 40), cost-effectiveness analyses (34, 36, 37) and cost-utility
30 analysis (39). Two papers reported a cost of care (40) and cost utility analysis (39) from the
31 same study. The outcome measure utilised across all three cost-effectiveness studies was
32 length of hospital stay.
33
34
35
36
37
38
39
40
41

42 *Study outcomes*

43
44 The identified studies reported a reduction in costs for OMT when compared with standard
45 care for the management of neonatal preterm birth recovery (34), lumbar disc herniation-
46 associated sciatica (49), and posterolateral postthoractomy recovery (36), but not for the
47 management of neck or back pain. The 'cost of treatment' studies identified either direct
48 cost-savings in the case of lumbar disc herniation-associated sciatica (reflecting a savings of
49 £300 per patient) (33), or a reduced cost of care when patients with low back pain (35) or
50 migraine headache (38) were treated by an osteopathic physician as compared to standard
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

care. Reduction in the length of hospital stay was reported in posterolateral post-thoracotomy recovery (for patients with lung decortication only) (-6.4 days) (36), pancreatitis (-4.5 days) (37), and neonatal preterm birth recovery (-5.9 days) (34). The latter study involving preterm infants was the only study to extrapolate a cash value to this outcome, proposing a net saving of -€2724.91 per infant (34). The only cost-utility analysis identified reported improved pain and quality of life in patients with neck or back pain (39, 40) at a cost of £3760 per quality-adjusted life year (QALY) gained.

Critical appraisal of economic analysis of osteopathic manipulative techniques

There were substantial differences in the quality of reporting of the six included papers (from five discrete studies) evaluating the cost-effectiveness of osteopathic manual therapies when assessed against the CHEERS guidelines (see Table 4). Two papers were unable to be assessed against CHEERS guidelines as they failed to report monetary outcomes from their economic analyses (36, 37). The majority of the included papers effectively reported the background and objectives (5/6), target population and subgroups (5/6), estimation of resources and costs (5/6), and the discussion of the findings (5/6). The areas of greatest weakness across the included studies were the identification of study perspective (1/6), discount rate (1/6), and assumptions applied to the economic analysis (1/6). The highest quality reporting was found in the two papers by Williams et al (39, 40) which met 18 and 16 of the 23 CHEERS criteria, respectively; however, these still fell short in some criteria, although different weaknesses were identified in each paper. In contrast, the reporting of the economic evaluations by Burton et al (33) and Schabert and Crow (38) only met 5 and 7 of the required 23 criteria, respectively.

DISCUSSION

This paper represents the first systematic review and critical appraisal of comparative effectiveness and health economic research of OMT. The findings point toward an insufficient quantity and inadequate quality of comparative effectiveness and cost-effectiveness research to effectively inform OMT policy and practice. Despite positive

findings across a number of areas, including the cost-effective management of low back pain (39, 40) and preterm neonate recovery (34), the majority of studies provide incomplete data or lack sufficient rigour to be integrated into evidence-based policy decisions (24). Similarly, CER suggests OMT may be as effective as standard care for the management of low back (42) and neck (47) pain; however, studies need to be replicated in different settings and jurisdictions to verify current findings and provide the level of evidence required to inform practice change within the broader health system (18). Given the relatively high use of OMT amongst individuals with conditions such as back pain (10), as well as the use of OMT by pregnant women (9), it is paramount that the abovementioned findings be replicated to ensure that clear guidance can be given to these vulnerable populations accessing OMT.

The high level of heterogeneity across the identified studies significantly limits our ability to draw firm conclusions about the comparative effectiveness and economic value of OMT when compared with other available health services. This highlights the need for clearer guidance on the design, implementation and reporting of osteopathic research. Guidance on comparative effectiveness research, for instance, should be attentive to standard research reporting requirements (including descriptions of treatment), quality outcome measures, appropriate comparator interventions, and suitable blinding and allocation concealment procedures. Guidance on economic evaluations, on the other hand, should focus on clearly defining the study perspective, discount rate and assumptions of the analysis. These recommendations are explored in greater detail in the final section of this discussion.

The majority of included papers reported results from research conducted in the US. This is likely to impact the applicability and generalizability of the findings to other jurisdictions.

Notably, it is argued that general osteopathic practice in the US is substantially different to the rest of the world. This is because osteopathic practitioners in the US are trained as physicians before specialising in OMT; by contrast, European and Australasian osteopathic training focuses on OMT, and osteopathic training does not result in licensure to practice medicine as a physician (1). The reviewed studies focused specifically on the administration

of OMT by osteopaths in clinical settings, and as such there may be potential for transferability of findings to countries where osteopaths practice as allied health professionals or complementary therapists (1, 5). However, there remains a clear need to verify the outcomes of these studies in different professional and health care contexts.

Research gaps and recommendations for future research

The critical appraisal of included papers highlights the need for increased CER and economic analyses in OMT, as well as the replication of such studies; it also alludes to the need to improve the quality of future OMT research to ensure findings can inform policy and practice. We propose a number of key areas which should be considered in the design of future studies of OMT.

Firstly, researchers need to systematically collect and report the details of OMT used in comparative effectiveness studies. Whilst the purpose of pragmatic research is to reflect real life practice as closely as possible, documenting and reporting the specific techniques utilised in osteopathic research would be highly beneficial for practitioners, educators and researchers. Not only would such detailed reporting of osteopathic interventions facilitate the translation of research evidence into practice, education and policy, but it would also allow inferential statistical analyses to test the potential relationships between specific techniques and overall effectiveness of OMT. As such, future osteopathy comparative effectiveness research would benefit from complying with intervention reporting guidelines such as the Template for Intervention Description and Replication (TIDieR) checklist and guide (50) or the CONSORT extension for pragmatic trials (51).

Secondly, future OMT studies should incorporate more sensitive and nuanced statistical analyses. Despite most studies collecting data on important confounding and effect modifying variables such as body mass index and gender, few analyses controlled for these variables. Similarly, none of the identified CER studies reported analyses of the primary results in an attempt to test and verify the key assumptions of the study. For example, if regression analysis is used to assess the effectiveness of the intervention, then this

1 assumes treatment does not change throughout the study for any one individual and as
2 such, their responsiveness to treatment is also consistent. Use of time-dependent regression
3 would assist in verifying the validity of the study outcome in this case (52). Similarly, missing
4 data, a common feature of comparative effectiveness studies, was not appropriately
5 managed within many of these studies. Future studies need to evaluate the extent of
6 missing data and its impact on the analysis (52).
7
8
9
10
11
12

13 The design and reporting of future economic evaluations of OMT can also be improved. The
14 economic perspective of the analysis should be described and justified, i.e. the a priori
15 decisions as to whether the 'cost' of the intervention will be restricted to government and
16 third party funders or will be broadened to include the cost to patients, their families and
17 society in general (53). Providing a clearer perspective will enable key stakeholders to make
18 rational decisions about the allocation of scarce healthcare resources, such as the allocation
19 of funds to support the provision of osteopathic services. Likewise, the currency, price date
20 and conversion rate must be included in future economic studies of OMT as this impacts on
21 the transferability of the analysis to other jurisdictions, as well as the relevance of the
22 findings over time. These issues can be overcome by future research groups undertaking
23 studies involving economic evaluations of osteopathy by complying with the CHEERS
24 reporting statement (32) when reporting findings.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 CONCLUSIONS

42 Comparative effectiveness and health economic studies offer valuable insights into health
43 services that can inform evidence-based policy and practice. Despite the diverse regional
44 presence of osteopathy and the practice of OMT throughout the world, limited research
45 focusing upon OMT has employed either of these study methodologies to date. There is a
46 need for researchers and the broader osteopathic community to support the advancement of
47 rigorous and robust comparative effectiveness and health economic research that reflects
48 osteopathic practice if this area of health care provision is to advance its role and place
49 within health care systems around the world.
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Conflicts of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

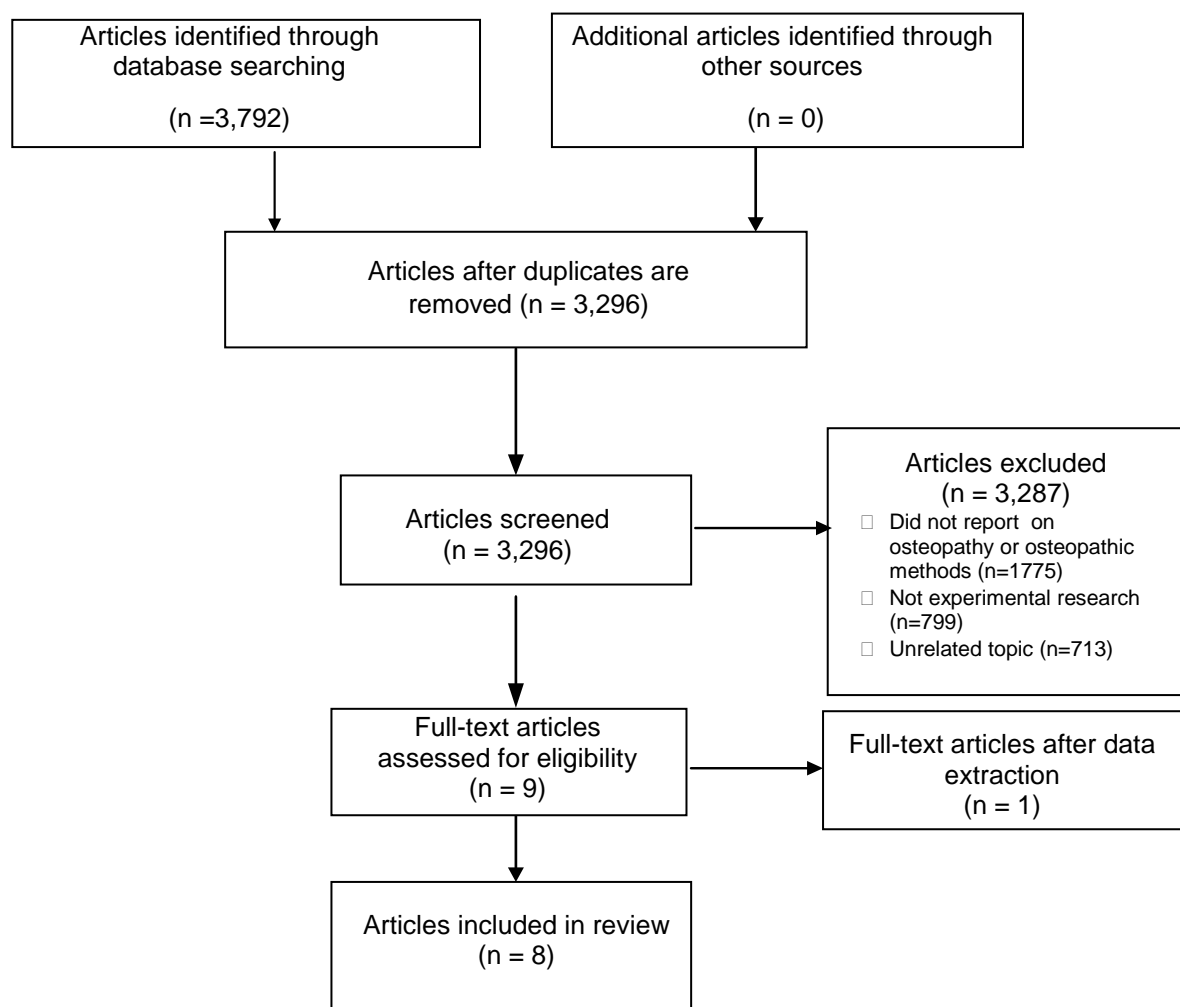


Figure 1: PRISMA Flow chart for articles reporting comparative effectiveness of osteopathic manipulative treatment

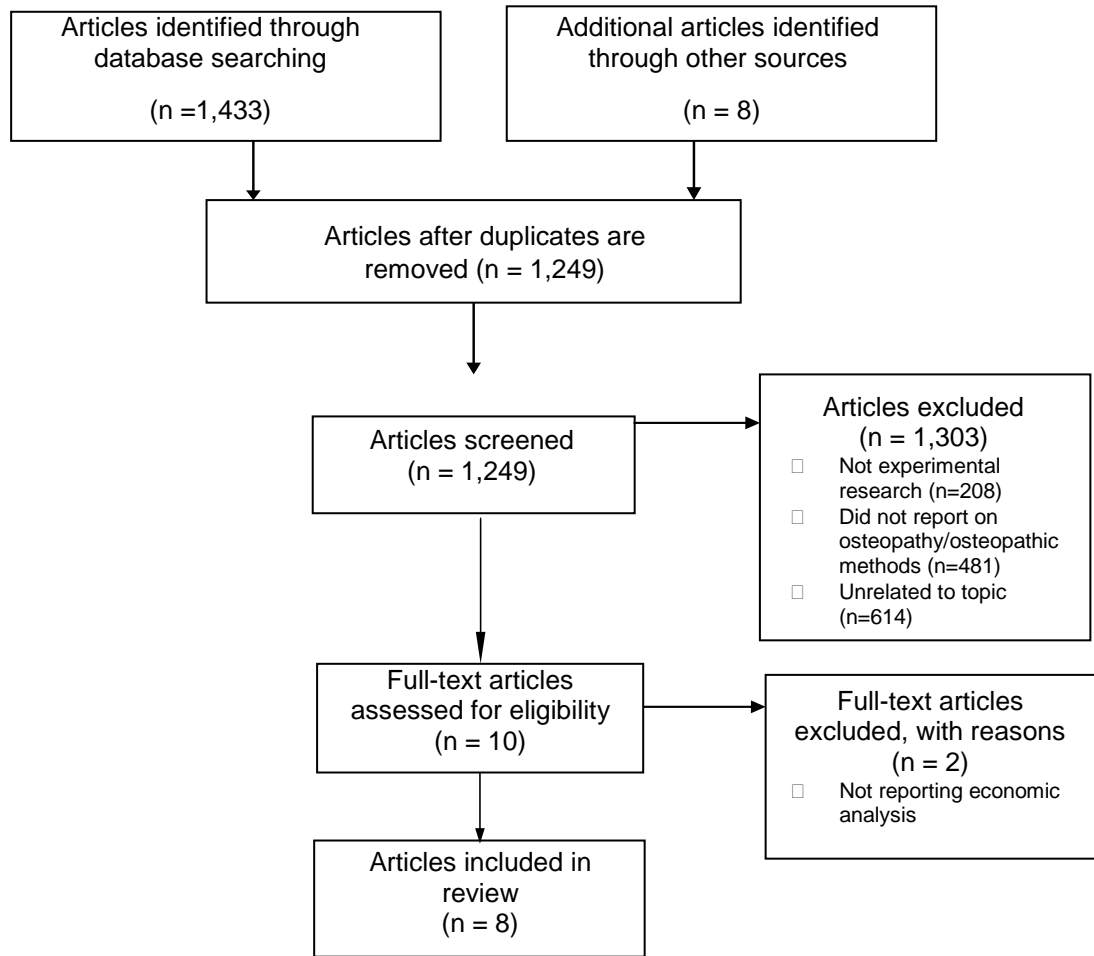


Figure 2: PRISMA Flow chart for articles reporting health economic analysis of osteopathic manipulative treatment

Table 1: Characteristics of included studies examining the cost or comparative effectiveness of osteopathic manipulative treatment.

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Comparative effectiveness studies								
Andersson et al (42)	1999	United States	Randomised controlled trial (2 arms)	Patients (20-59 yrs) of a health maintenance organisation; n=178	Low back pain (>3 wks but <6 months duration)	Osteopathic manipulation OR standard allopathic treatment	Visual-analogue pain scale (0-100); Roland-Morris; Oswestry	Follow-up 12 wks: No significant difference between groups in any primary outcome measure. Osteopathic group used less medication (analgesics, anti-inflammatory, muscle relaxants) ($P < 0.001$) and less physical therapy ($P < 0.05$).

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Licciardone et al (46)	2002	United States	Randomised controlled trial (3 arms)	Patients (18-69 yrs) of a university based clinic; n=91	Nonspecific low back pain (>3 months duration)	Osteopathic manipulative treatment OR sham manipulation, OR a no-intervention control group. All patients were allowed to continue their usual care for low back pain.	SF-36; 10-cm visual analog scale for overall back pain; Roland–Morris; Lost work or school days because of back pain; Satisfaction with back care	Follow-up 6 months: There were no significant benefits with osteopathic manipulative treatment, as compared with sham manipulation. Both active and sham manipulation appear to provide some benefits when used in addition to usual care for the treatment of chronic nonspecific low back pain (e.g. greater improvements in back pain and physical functioning and greater satisfaction of care).

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Duncan et al (44)	2004	United States	Randomised controlled trial (3 arms); (and a co-study with 1 arm)	Pediatric patients (11 months to 12 yrs) at a children's clinic for rehabilitation services; n=50 (co-study n=19)	Spastic cerebral palsy	Wait-list control; OR Osteopathic manipulation; OR Acupuncture. (Co-study combined osteopathic manipulation and acupuncture.) (Intervention treatments complemented the patients' standard care.)	Parents were asked: "Did you note any changes in your child as a result of the therapies, and if so, what were the changes?" Parents' perception of their child's level of muscle stiffness and their child's level of happiness on 2 separate visual log scales, 100 millimeters in length.	Follow-up 24 wks: 2 of 17 parents reported positive gains while their child was in a wait-list control period (but all 17 reported gains while in the treatment phase of the study; Twenty-one of the 23 parents of the children in the osteopathic group reported improvement in their child during the course of therapies; All of the 19 parents of children in the acupuncture group reported improvements in their child.

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
McReynolds & Sheridan (47)	2005	United States	Randomised controlled trial (2 arms)	Patients (18 to 50 yrs) in emergency department; n=58	Acute neck pain (<3 wks duration)	Intra muscular injection with Ketoralac (30 ml); OR Osteopathic manipulative treatment (5 min)	11-point numerical rating scale for pain	Follow-up one hour post treatment: Both groups had significant reduction in pain intensity but there was no significant difference between the OMT and ketorolac study groups (P=.10)
Anderson & Seniscal (41)	2006	Canada	Randomised controlled trial (2 arms)	Patients (>16 yrs) recruited from ads and flyers; n=29	Tension type headache (frequent/ chronic/ probable)	Progressive muscular relaxation; OR Progressive muscular relaxation plus 3 osteopathic treatments	Headache diary	Follow-up 4 to 5 weeks post treatment initiation (6 to 7 wks from baseline): Number of headache free days/wk improved with osteopathy (P = .016). There was no significant difference in headache intensity (P = .264).

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Chown et al (43)	2008	United Kingdom	Randomised clinical trial (3 arms)	Patients (18-65 yrs) referred to physiotherapy; n=239	Low back pain (>3 months duration)	Group exercise physiotherapy; OR One-to-one physiotherapy; OR One-to-one Osteopathy	Oswestry Disability Index (ODI) was the primary outcome	Follow-up 6 wks: All three treatments indicated comparable reductions in mean (95% confidence intervals) ODI: group exercise, -4.5 (-0.9 to -8.0); physiotherapy, -4.1 (-1.4 to -6.9); and osteopathy, -5.0 (-1.6 to -8.4).

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Duncan et al (45)	2008	United States	Pilot randomised controlled trial (3 arms)	Pediatric patients (20 months to 12 yrs) at a children's clinic for rehabilitation services; n=55	Spastic cerebral palsy	Wait-list control; OR Osteopathic Manipulative Treatment; OR Acupuncture. (Intervention treatments complemented the patients' standard care.)	11 outcome variables	Follow-up 24 wks: statistically significant improvement in two mobility measures for patients who received OMT—the total score of Gross Motor Function Measurement and the mobility domain of Functional Independence Measure for Children (P<.05). No statistically significant improvements were seen among patients in the acupuncture treatment arm.

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Wahl et al (48)	2008	United States	Randomised, placebo-controlled, two-by-two factorial trial (4 arms)	Pediatric patients (12 to 60 months); n=90	Recurrent otitis media (otitis-prone children)	True osteopathic manipulative treatment (OMT) plus placebo Echinacea; OR Echinacea plus sham OMT; OR True echinacea plus true OMT; Double placebo (placebo Echinacea plus Sham OMT)	Prevention of acute otitis media (risk of having at least one episode of acute otitis media during 6-month follow-up compared to placebo/sham)	Follow-up 6 months: No interaction was found between <i>Echinacea purpurea</i> and OMT. <i>E.purpurea</i> was associated with a borderline increased risk of having at least one episode of acute otitis media during 6-month follow-up compared to placebo (65% versus 41%; relative risk, 1.59, 95% CI 1.04, 2.42). OMT did not significantly affect risk compared to sham (44% versus 61%; relative risk, 0.72, 95% CI 0.48, 1.10).
Economic analyses								
Radjeski, Lumley and Cantieri (37)	1998	United States	Randomised-controlled trial;	Hospital in-patients; n=14	Pancreatitis	Standard care	Length of hospital stay	Average length of stay reduced by 4.5 days (p=.039)

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Burton, Tillotson and Cleary (49)	2000	United Kingdom	Randomised-controlled trial	Hospital in-patients; n=30	Lumbar disc herniation-associated sciatica	Chemo-nucleolysis	Cost of treatment	Cost savings of £300 per patient with no difference in pain outcomes between groups
Williams et al (40)	2003	United Kingdom	Randomised-controlled trial	Osteopathy clinic outpatients; n=201	Neck or Back pain (2-12 weeks duration)	Standard GP care	Cost of treatment	Increased health care costs (£65) alongside improved pain and QoL measures
Williams et al (39)	2004	United Kingdom	Randomised-controlled trial	Osteopathy clinic outpatients; n=201	Neck or Back pain (2-12 weeks duration)	Standard GP care	Cost utility	£3760 per QALY gained as a result of treatment.

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Crow and Willis (35)	2009	United States	Retrospective clinic audit	Hospital patients; n=1556	Low back pain (<6 months duration)	Standard care	Cost of treatment	No difference in total cost per episode of care but reduced costs for radiology (<.0001) and prescription medications (<.001).
Schabert and Crow (38)	2009	United States	Retrospective clinic audit	Hospital clinic outpatients; n=1427	Migraine headache	Standard care OR osteopathic care without manipulative treatment	Cost of treatment	Lower cost per office visit compared with MD but not compared with DO consults which exclude manipulative treatment
Cerritelli et al (34)	2013	Italy	Randomised-controlled trial	Preterm newborns admitted to Neonatal Intensive Care Unit; n=110	Neonatal preterm birth recovery	Standard paediatric care	Length of hospital stay	Length of stay reduced by 5.9 days with OMT (p<.0001); reduced cost estimates (-€2724.91, p<.0001); no impact on weight gain.

Author (Year)	Year	Country	Study design and duration	Participants, setting and sample	Condition examined	Interventions (active and control arms)	Outcome measures and time-points	Summary of findings (effectiveness of OMT)
Fleming et al (36)	2015	United States	Retrospective clinic audit;	Hospital inpatients; n=38	Posterolateral postthoractomy recovery	Standard care	Length of hospital stay	Length of stay reduced for patients having lung decortication (-6.4 days, p=.005) but not others

Table 2: Rating of study bias using Cochrane Collaboration risk of bias tool and PRECIS-2 rating of comparative effectiveness studies

First Author, Year	Random sequence generation: selection bias	Allocation concealment: selection bias	Blinding of participants, personnel: performance bias	Blinding of outcome assessment: detection bias	Incomplete outcome data: attrition bias	Selective outcome reporting: reporting bias	Other sources of bias	Explanatory or Observational study (PRECIS-2)
McReynolds & Sheridan (47)	Low	Unclear	High	High	Low	Unclear	Unclear	33
Andersson et al (42)	Low	Unclear	High	Unclear	Low	Unclear	Low	30

Chown et al (43)	Low	Unclear	High	High	High	Unclear	Unclear	28
Duncan et al (44)	Unclear	Unclear	High	High	Unclear	High	High	28
Anderson & Seniscal (41)	Low	High	High	High	Unclear	High	Unclear	26
Duncan et al (45)	Low	Low	Unclear	Low	High	Unclear	High	25
Wahl et al (48)	Low	Low	Low	Low	Unclear	Unclear	Unclear	25
Licciardone et al (46)	Unclear	Unclear	High	Unclear	High	Unclear	Low	20

Table 3. Compliance of comparative effectiveness related osteopathic papers with the Good ReseArch for Comparative Effectiveness (GRACE) statement checklist

Section/item	Andersson et al (42)	Licciardone et al (46)	Duncan et al (44)	McReynolds & Sheridan (47)	Anderson & Seniscal (41)	Chown et al (43)	Duncan et al (45)	Wahl et al (48)
Data (D1-D6)								
D1. Details of treatment adequately recorded	-	-	-	-	-	-	-	-
D2. Primary outcomes adequately recorded	X	X	-	X	X	X	X	-
D3. Primary clinical outcome(s) measured objectively	X	X	-	X	X	X	X	-
D4. Primary outcomes validated/ adjudicated	X	X	-	X	X	X	X	-
D5. Primary outcome(s) measured or identified in an equivalent manner between the treatment/intervention group and the comparison group(s)	X	X	X	X	n/a	X	X	X
D6. Important covariates (known confounders/effect modifiers) available and recorded	X	X	X	X	X	X	X	X
Methods (M1-M5)	X	X		X		X		
M1. Study population restricted to new initiators of treatment	X	X	-	X	-	X	-	-
M2. Concurrent comparators or justification of historical comparisons group(s)	X	X	X	X	n/a	X	X	X

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

M3. Important covariates/confounding and effect modifying variables taken into account in the design and/or analysis	X	X	-	X	X	-	-	-
M4. Classification of exposed and unexposed person-time free of “immortal time bias”	X	X	X	X	X	X	-	-
M5. Meaningful analyses conducted to test key assumptions on which primary results are based	-	-	-	-	-	-	-	-
Total	10	10	4	10	8	9	6	3

Table 4: Compliance of health economic related osteopathic papers with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement checklist.*

Section/item	Burton, Tillotson and Cleary (2000)	Williams et al (2003)	Williams et al (2004)	Crow and Willis (2009)	Schabert and Crow (2009)	Cerritelli et al (2012)
Title and abstract						
Title	-	-	X	X	X	-
Abstract	-	X	X	-	-	-
Introduction						
Background and objectives	-	X	X	X	X	X
Methods						
Target population and subgroups	X	X	X	X	-	X
Setting and location	-	-	X	X	X	X
Study perspective	-	-	X	-	-	-
Comparators	X	X	X	X	X	X
Time horizon	-	-	X	X	-	X
Discount rate	-	-	X	-	-	-
Choice of health outcomes	-	X	X	-	-	X
Measurement of effectiveness	-	X	X	-	-	X
Estimating resources and costs	X		X	X	X	X
Currency, price date, and conversion	-	X	-	-	-	X
Choice of model	-	X	X	-	-	-

Assumptions	-	X	-	-	-	-
Analytical methods	-	X	-	X	-	X
Results						
Study parameters	-	X	X	X	-	X
Incremental costs and outcomes	-	X	X	-	-	-
Characterising uncertainty	-	X	X	-	-	-
Characterising heterogeneity	-	X	X	-	X	-
Discussion						
Study findings, limitations, generalizability, and current knowledge	-	X	X	X	X	X
Other						
Source of funding	X	X	-	X	-	X
Conflicts of interest	-	-	-	X	-	X
TOTAL (out of 23)	5	16	18	13	7	14

*Appraisal using CHEERS guidelines was not undertaken for Radjeski, Lumley and Cantieri (37) and Fleming et al. (36) as they did not provide monetary outcome data in their analyses

1. Osteopathy International Alliance. History and Current Context of the Osteopathic Profession. <http://wp.oialliance.org/wp-content/uploads/2013/07/oia-status-report-history-context-of-osteopathic-profession.pdf>. 2012.
2. Murthy V, Sibbritt D, Adams J. An integrative review of complementary and alternative medicine use for back pain: A focus on prevalence, reasons for use, influential factors, self-perceived effectiveness and communication. *The Spine Journal*. 2015.
3. Dalla Libera D, Colombo B, Pavan G, Comi G. Complementary and alternative medicine (CAM) use in an Italian cohort of pediatric headache patients: the tip of the iceberg. *Neurological Sciences*. 2014;35(1):145-8.
4. Frawley J, Sundberg T, Steel A, Sibbritt D, Broom A, Adams J. Prevalence and characteristics of women who consult with osteopathic practitioners during pregnancy; a report from the Australian Longitudinal Study on Women's Health (ALSWH). *Journal of Bodywork and Movement Therapies*. 2015.
5. Thomson OP, Petty NJ, Moore AP. Clinical decision-making and therapeutic approaches in osteopathy—a qualitative grounded theory study. *Manual therapy*. 2014;19(1):44-51.
6. Xue CC, Zhang AL, Lin V, Myers R, Polus B, Story DF. Acupuncture, chiropractic and osteopathy use in Australia: a national population survey. *BMC Public Health*. 2008;8(1):105.
7. Licciardone JC. Awareness and use of osteopathic physicians in the United States: results of the Second Osteopathic Survey of Health Care in America (OSTEOSURV-II). *The Journal of the American Osteopathic Association*. 2003;103(6):281-9.
8. Sibbritt D, Adams J, Young AF. A profile of middle-aged women who consult a chiropractor or osteopath: findings from a survey of 11,143 Australian women. *Journal of manipulative and physiological therapeutics*. 2006;29(5):349-53.
9. Steel A, Adams J, Sibbritt D, Broom A, Gallois C, Frawley J. Utilisation of complementary and alternative medicine (CAM) practitioners within maternity care provision: results from a nationally representative cohort study of 1,835 pregnant women. *BMC pregnancy and childbirth*. 2012;12(1):146.
10. Ong CK, Doll H, Bodeker G, Stewart-Brown S. Use of osteopathic or chiropractic services among people with back pain: a UK population survey. *Health & social care in the community*. 2004;12(3):265-73.
11. Licciardone JC, Brimhall AK, King LN. Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials. *BMC musculoskeletal disorders*. 2005;6(1):43.
12. Schwerla F, Kaiser AK, Gietz R, Kastner R. Osteopathic treatment of patients with long-term sequelae of whiplash injury: effect on neck pain disability and quality of life. *The Journal of Alternative and Complementary Medicine*. 2013;19(6):543-9.
13. Franke H, Franke J-D, Fryer G. Osteopathic manipulative treatment for chronic nonspecific neck pain: A systematic review and meta-analysis. *International Journal of Osteopathic Medicine*. 2015.
14. Zanotti E, Berardinelli P, Bizzarri C, Civardi A, Manstretta A, Rossetti S, et al. Osteopathic manipulative treatment effectiveness in severe chronic obstructive pulmonary disease: a pilot study. *Complementary therapies in medicine*. 2012;20(1):16-22.
15. Florance B-M, Frin G, Dainese R, Nébot-Vivinus M-H, Barjoan EM, Marjoux S, et al. Osteopathy improves the severity of irritable bowel syndrome: a pilot randomized sham-controlled study. *European journal of gastroenterology & hepatology*. 2012;24(8):944-9.
16. Attali TV, Bouchoucha M, Benamouzig R. Treatment of refractory irritable bowel syndrome with visceral osteopathy: Short-term and long-term results of a randomized trial. *Journal of digestive diseases*. 2013;14(12):654-61.
17. Posadzki P, Lee MS, Ernst E. Osteopathic manipulative treatment for pediatric conditions: a systematic review. *Pediatrics*. 2013;131(5):e1233-9.

18. Zaorsky M, Showalter M, editors. How will Comparative Effectiveness Research Influence Clinical Decision Making? The Medicine Forum; 2012.
19. Winter AC, Colditz GA. Clinical trial design in the era of comparative effectiveness research. 2014.
20. Insitute of Medicine. Initial National Priorities for Comparative Effectiveness Research Washington DC: National Academic Press; 2009 [cited 2016 8 Jan]. Available from: <http://www.nap.edu/catalog/12648.html>.
21. Sox HC, Goodman SN. The methods of comparative effectiveness research. Annual review of public health. 2012;33:425-45.
22. Standaert CJ, Friedly J, Erwin MW, Lee MJ, Rehtine G, Henrikson NB, et al. Comparative effectiveness of exercise, acupuncture, and spinal manipulation for low back pain. Spine. 2011;36(21 SUPPL.):S120-S30.
23. Menke JM. Do manual therapies help low back pain? A comparative effectiveness meta-analysis. Spine. 2014;39(7):E463-E72.
24. Goeree R, Diaby V. Introduction to health economics and decision-making: Is economics relevant for the frontline clinician? Best Practice & Research Clinical Gastroenterology. 2013;27(6):831-44.
25. Michaleff Z, Lin C-W, Maher C, van Tulder M. Spinal manipulation epidemiology: systematic review of cost effectiveness studies. Journal of Electromyography and Kinesiology. 2012;22(5):655-62.
26. Tsertsvadze A, Clar C, Court R, Clarke A, Mistry H, Sutcliffe P. Cost-effectiveness of manual therapy for the management of musculoskeletal conditions: a systematic review and narrative synthesis of evidence from randomized controlled trials. Journal of manipulative and physiological therapeutics. 2014;37(6):343-62.
27. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9.
28. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: Wiley Online Library; 2008.
29. Higgins J, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 [updated March 2011]. Cochrane Handbook for Systematic Reviews of Interventions Version. 2011;5.
30. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. bmj. 2015;350:h2147.
31. Dreyer NA, Schneeweiss S, McNeil BJ, Berger ML, Walker AM, Ollendorf DA, et al. GRACE principles: recognizing high-quality observational studies of comparative effectiveness. The American journal of managed care. 2010;16(6):467-71.
32. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. BMC medicine. 2013;11(1):1.
33. Burton AK, Tillotson KM, Cleary J. Single-blind randomised controlled trial of chemonucleolysis and manipulation in the treatment of symptomatic lumbar disc herniation. European Spine Journal. 2000;9(3):202-7.
34. Cerritelli F, Pizzolorusso G, Ciardelli F, La Mola E, Cozzolino V, Renzetti C, et al. Effect of osteopathic manipulative treatment on length of stay in a population of preterm infants: a randomized controlled trial. BMC Pediatr. 2013;13:65.
35. Crow WT, Willis DR. Estimating cost of care for patients with acute low back pain: a retrospective review of patient records. JAOA: Journal of the American Osteopathic Association. 2009;109(4):229-33.
36. Fleming RK, Snider KT, Blanke KJ, Johnson JC. The effect of osteopathic manipulative treatment on length of stay in posterolateral postthoracotomy patients: A retrospective case note study. International Journal of Osteopathic Medicine. 2015;18(2):88-96.

37. Radjieski JM, Lumley MA, Cantieri MS. Effect of osteopathic manipulative treatment of length of stay for pancreatitis: a randomized pilot study. *J Am Osteopath Assoc.* 1998;98(5):264-72.
38. Schabert E, Crow WT. Impact of osteopathic manipulative treatment on cost of care for patients with migraine headache: a retrospective review of patient records. *J Am Osteopath Assoc.* 2009;109(8):403-7.
39. Williams NH, Edwards RT, Linck P, Muntz R, Hibbs R, Wilkinson C, et al. Cost-utility analysis of osteopathy in primary care: results from a pragmatic randomized controlled trial. *Family Practice* 2004 Dec;21(6):643-650. 2004.
40. Williams NH, Wilkinson C, Russell I, Edwards RT, Hibbs R, Linck P, et al. Randomized osteopathic manipulation study (ROMANS): pragmatic trial for spinal pain in primary care. *Family Practice* 2003 Dec;20(6):662-669. 2003.
41. Anderson RE, Seniscal C. A comparison of selected osteopathic treatment and relaxation for tension-type headaches. *Headache: The Journal of Head & Face Pain.* 2006;46(8):1273-80.
42. Andersson GB, Lucente T, Davis AM, Kappler RE, Lipton JA, Leurgans S. A comparison of osteopathic spinal manipulation with standard care for patients with low back pain. *N Engl J Med.* 1999;341(19):1426-31.
43. Chown M, Whittamore L, Rush M, Allan S, Stott D, Archer M. A prospective study of patients with chronic back pain randomised to group exercise, physiotherapy or osteopathy. *Physiotherapy.* 2008;94(1):21-8.
44. Duncan B, Barton L, Edmonds D, Blashill BM. Parental perceptions of the therapeutic effect from osteopathic manipulation or acupuncture in children with spastic cerebral palsy. *Clinical Pediatrics.* 2004;43(4):349-53.
45. Duncan B, McDonough-Means S, Worden K, Schnyer R, Andrews J, Meaney FJ. Effectiveness of osteopathy in the cranial field and myofascial release versus acupuncture as complementary treatment for children with spastic cerebral palsy: a pilot study. *JAOA: Journal of the American Osteopathic Association.* 2008;108(10):559-70.
46. Licciardone J, Gamber R, Cardarelli K. Patient satisfaction and clinical outcomes associated with osteopathic manipulative treatment. *JAOA: Journal of the American Osteopathic Association.* 2002;102(1):13.
47. McReynolds TM, Sheridan BJ. Intramuscular ketorolac versus osteopathic manipulative treatment in the management of acute neck pain in the emergency department: a randomized clinical trial. *J Am Osteopath Assoc.* 2005;105(2):57-68.
48. Wahl RA, Aldous MB, Worden KA, Grant KL. Echinacea purpurea and osteopathic manipulative treatment in children with recurrent otitis media: a randomized controlled trial. *BMC Complement Altern Med.* 2008;8:56.
49. Burton AK, Tillotson KM, Cleary J. Single-blind randomised controlled trial of chemonucleolysis and manipulation in the treatment of symptomatic lumbar disc herniation. *Eur Spine J.* 2000;9(3):202-7.
50. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ.* 2014;348.
51. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *Bmj.* 2008;337:a2390.
52. Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM. Developing a protocol for observational comparative effectiveness research: a user's guide: Government Printing Office; 2013.
53. Drummond M, Weatherly H, Ferguson B. Economic evaluation of health interventions. *BMJ.* 2008;337.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	16-17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	18 (Table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

*Author Checklist

AUTHOR CHECKLIST *Authors of all papers reporting clinical research should submit this checklist together with their manuscript and the Reporting Guideline Checklist found on the EQUATOR site (<http://www.equator-network.org/>).*

This checklist identifies recognised guidelines for scientific reporting, which authors should use to prepare their manuscript (*required for systematic reviews and original research*)

Standards of reporting		Guideline referred to	Checklist submitted**
<p>The editors require that manuscripts adhere to recognised reporting guidelines relevant to the research design used. These identify matters that should be addressed in your paper. Please indicate which guidelines you have referred to.</p> <p>These are not quality assessment frameworks and your study need not meet all the criteria implied in the reporting guideline to be worthy of publication in the MATH. The checklists do identify essential matters that should be considered and reported upon. For example, a controlled trial may or may not be blinded but it is important that the paper identifies whether or not participants, clinicians and outcome assessors were aware of treatment assignments.</p> <p>**You are also required to submit a checklist from the appropriate reporting guideline (available on the EQUATOR website (http://www.equator-network.org/) together with your paper as a guide to the editors.</p> <p><i>Reporting guidelines endorsed by MATH are listed below:</i></p>			
Randomised (and quasi-randomised) controlled trial	CONSORT – Consolidated Standards of Reporting Trials http://www.equator-network.org/reporting-guidelines/consort/		
Study of Diagnostic accuracy / assessment scale	STARD Standards for the Reporting of Diagnostic Accuracy studies http://www.equator-network.org/reporting-guidelines/stard/		
Systematic Review of Controlled Trials	PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses http://www.equator-network.org/reporting-guidelines/prisma/	X	X
Observational cohort, case control and cross sectional studies	STROBE S trengthening the R eporting of O bservational Studies in E pidemiology http://www.equator-network.org/reporting-guidelines/strobe/		
Case Reports	CARE - Case Reports - http://www.care-statement.org/downloads/CAREchecklist-English.pdf		
Statistical reporting	SAMPL - guidelines for statistical reporting – <i>no checklist exists currently but authors are encouraged to view the guidelines on the EQUATOR website http://www.equator-network.org/reporting-guidelines/sampl/</i>		
	<i>Qualitative researchers might wish to consult the guideline listed below</i>		
Qualitative studies	COREQ: Consolidated criteria for reporting qualitative research (http://www.equator-network.org/reporting-guidelines/coreq/)		
Other (please give source)			
Not applicable (please elaborate)			