NCCHTA

12 March 2009

THE EFFECTIVENESS AND COST EFFECTIVENESS OF MANAGEMENT STRATEGIES FOR SCIATICA: SYSTEMATIC REVIEW AND ECONOMIC MODEL

PROTOCOL
22/01/09

DETAILS OF REVIEW TEAM

Correspondence to:
Ms Ruth Lewis
Department of Primary Care & Public Health
Cardiff University
North Wales Clinical School / School of Medicine
Gwenfro Building, Unit 6-7
Wrexham Technology Park
Wrexham LL13 7YP
Tel: 01978 727340
e-mail: lewisr17@cardiff.ac.uk

Other members of the review team:
Dr Nefyn Williams, Clinical Senior Lecturer, Cardiff University
Dr. Hosam El-Din Matar, Research Associate, Cardiff University
Dr Nafees Din, Research Associate, Cardiff University
Dr John Belcher, Lecturer in Statistics, Cardiff University
Dr Alex Sutton, Reader in Medical Statistics, Leicester University
Professor Kim Burton, Director of the Spinal Research Unit, University of Huddersfield
Professor Ceri Phillips, Professor of Health Economics, Swansea University
Dr Deborah Fitzsimmon, Senior Lecturer in Clinical Research (Nursing), Swansea University
Ms Maggie Hendry, Research Fellow, Cardiff University
Professor Clare Wilkinson, Professor of General Practice, Cardiff University
Mr Ian Rickard, Clinician and Commissioner of health and social services, (Patient representative)
Mr Ian Braithwaite, Consultant Spinal Surgeon, Chester NHS Trust
Dr Robin Chakraverty, Musculoskeletal Physician, Royal Orthopedic Hospital, Birmingham

1. INTRODUCTION

Research is needed to identify the most clinical and cost-effective management strategies for sciatica. Many treatment modalities for sciatica have been evaluated in placebo controlled trials (or usual care used as the comparator), and the evidence relating to the direct comparison of numerous treatment modalities are missing. In addition, in clinical practice a sequential stepped care approach, using different treatment modalities is considered useful. However, primary studies have tended to examine individual treatments given in isolation, rather than sequential, stepwise treatment provision. The optimum sequence of treatment modalities and what sequence is best for which patients are therefore not known. In order to evaluate this, comparative estimates of the effectiveness of the different interventions, conditional on the administration of previous interventions, is required. Multiple treatments may also be administered sequentially in the hope of additive effects in combined therapy, therefore the additive and interaction effects of multiple interventions also needs to be explored. Previous systematic reviews have found evidence for the effectiveness of invasive treatments such as epidural steroid injection, chemonucleolysis and lumbar discectomy, but found insufficient evidence to advise bed rest, keeping active, analgesia, intramuscular steroid injection or traction. None of the reviews made indirect comparisons across separate trials or examined cost-effectiveness. Previous economic evaluations that have been conducted vary quite considerably, and their value is limited to the perspective and setting for which they were undertaken. We therefore plan to undertake a systematic review of the effectiveness and cost-effectiveness of different management strategies for sciatica, which tries to address some of these issues. We will also develop a decision analytical model to assess the cost-effectiveness of different treatment modalities from the UK perspective.

2. RESEARCH OBJECTIVES

- To undertake a systematic review of the effectiveness and cost-effectiveness of different management strategies for sciatica.
- To synthesise the results using meta-analyses and a mixed treatment comparison (MTC) method.
- To construct an appropriate probabilistic decision analytic model to estimate costs per quality adjusted life year (QALY) gained for each treatment strategy.
- To make recommendations for clinical practice and commissioning in the UK NHS.

3. BACKGROUND

3.1 Definition of sciatica

Sciatica is a symptom defined as unilateral, well-localised leg pain, with a sharp, shooting or burning quality, that approximates to the dermatomal distribution of the sciatic nerve down the posterior lateral aspect of the leg, and normally radiates to the foot or ankle. It is often associated with numbness or paraesthesia in the same distribution.[1, 2] The symptom of sciatica is used by clinicians in different ways. Some refer to any leg pain referred from the back as sciatica; others prefer to restrict its use to pain originating from the lumbar nerve root. Some authors prefer to use the term ‘lumbar nerve root pain’ to distinguish it from referred leg pain.[3]

3.2 Epidemiology of sciatica

The lack of clarity in the definition of sciatica persists in the epidemiological literature. In the UK, the prevalence of 'sciatica suggesting a herniated lumbar disc' has been reported as 3.1% in men and 1.3% in women.[4] However, like most surveys, this study did not use strict criteria to diagnose sciatica. A large population survey in Finland which did, found a lifetime prevalence of 5.3% in men and 3.7% in women.[5] Sciatica accounts for less than 5% of the cases of low back pain presenting to primary care.[3] Some cohort studies have found that most cases resolve spontaneously with 30% having persistent troublesome symptoms at one year, with 20% out of work and 5-15% requiring surgery.[6, 7] However, another cohort found that 55% still had symptoms of sciatica two years later, and 53% after four years (which included 25% who had recovered after two years but had relapsed again by four years).[8] The cost of sciatica to society in the Netherlands in 1991 was estimated at US$ 128 million for hospital care, US$730 million for absenteeism and US$ 708 million for disablement.[9]

3.3 Pathological mechanism

Sciatica caused by lumbar nerve root pain usually arises from a prolapsed intervertebral disc, but also from spinal stenosis, or surgical scarring.[7] It was initially thought to occur predominantly as a result of compression of the nerve root,[10] leading to neural ischaemia, oedema, which would in turn lead to chronic inflammation, scarring and perineural fibrosis. However, it is now known that symptoms can occur in the absence of direct nerve root compression, possibly as a result of release of pro-inflammatory factors from the damaged disc. Pain occurs because of chronic, repetitive firing of the inflamed nerve root.[11, 12] Referred leg pain occurs because pain fibres from paraspinal structures and from the leg converge on interneurones in the spinal cord and brain, so that nociceptive input from painful paraspinal tissues is perceived as leg pain.

3.4 Clinical diagnosis

It has been claimed that nerve root pain can be distinguished from referred leg pain because it is unilateral, radiates below the knee, the leg pain is worse than the back pain, can be aggravated by coughing or sneezing, and has a segmental distribution. Important clinical signs include provocation tests for dural irritation, such as a limited straight leg raise (SLR) reproducing the leg pain, and compromised nerve root function leading to reduced power, sensation or reflexes in one nerve root.[3] A systematic review of the diagnostic value of history and physical examination in nerve root pain found that pain distribution was the only useful item in the history. The SLR test was the only sensitive sign in the physical examination, but had poor specificity; the crossed SLR test was the only specific sign, but had poor sensitivity.[13] However, another review found that there was no standard SLR procedure, no consensus on interpretation of results, no evidence of intra and inter-observer reliability, and its predictive value in lumbar intervertebral disc surgery was unknown. [14]

3.5 Treatments

A variety of surgical and non-surgical treatments have been used to treat sciatica and have been the subject of previous systematic reviews, the findings of which are summarised below. However, none of the reviews examined the cost-effectiveness of the various treatment modalities.

Two sets of guidelines on the management of sciatica from 1994 recommend initial conservative management with advice, reassurance and analgesia if there is no major or progressive motor weakness, and urgent referral for specialist assessment and investigation if symptoms are not resolving satisfactorily after six weeks.[2] If strong

physiologic evidence of a specific nerve root dysfunction with intervertebral disc herniation confirmed at corresponding level and side by findings on an imaging study, surgical options can be discussed. Standard discectomy or microdiscectomy is the surgical treatment of choice.[15] More recent guidelines have concentrated on non-specific low back pain, and have not discussed the management of sciatica. This review will inform the development of up to date management recommendations by other groups.

Bed rest and advice to stay active: Most cases resolve spontaneously and traditionally bed rest has been used. A Cochrane systematic review of bed rest[16] found that there was high quality evidence of little or no difference in pain or functional status between bed rest and staying active; moderate quality evidence of little or no difference in pain intensity between bed rest and physiotherapy, but small improvements in functional status with physiotherapy; moderate quality evidence of little or no difference in pain intensity or functional status between two to three and seven days bed rest. A Cochrane systematic review of advice to keep active reviewed the same trials comparing bed rest with activity and came to the same conclusions. Although there is no evidence to advise bed rest for sciatica, there is also very little evidence of benefit for advice to keep active.[17]

Analgesia: Most patients will obtain analgesic medication either prescribed or 'over the counter' from their pharmacist. A systematic review of conservative treatment for sciatica identified three randomised controlled trials (RCTs) that compared non-steroidal anti inflammatory drugs (NDAIDs) with a placebo tablet and found no evidence of efficacy.[18]

Intramuscular steroids: Part of the mechanism for producing nerve root pain is by release of pro-inflammatory factors from damaged discs, so administration of intramuscular corticosteroid steroid injections to reduce inflammation of the nerve root has a theoretical basis. The systematic review of conservative treatment for sciatica identified two RCTs comparing steroid injections with a placebo injection and found no evidence of efficacy.[18]

Traction: Traction is used relatively frequently to treat sciatica in North America, but less frequently in the UK, Eire and the Netherlands.[19, 20] A Cochrane systematic review found strong evidence that there was no significant difference between either continuous or intermittent traction versus placebo, sham or other treatments.[21]

Epidural steroids: Introduction of corticosteroids into the epidural space is a commonly used treatment for lumbar nerve root pain, with the rationale of reducing nerve root inflammation. It was performed on 47,665 occasions in the NHS in England in 2005/06.[22] A systematic review of epidural steroid injections compared with saline or local anaesthetic injection, or dry needling reported that six RCTs found epidural steroids to be better than a control treatment; six RCTs found them to be no better or worse. The methodological quality of these RCTs was criticised.[23] A further systematic review examined selective nerve root blocks, excluding epidurals given by the caudal route and found five RCTs, one of high quality, found moderate evidence that they were more effective than an a local anaesthetic or saline injection.[24] Since then a RCT funded by the HTA[25] found that epidural steroid injection resulted in a small, transient improvement in function and pain compared with placebo three weeks after injection, but no relative improvement after six weeks and one year. This RCT also performed a health economic analysis; none of the cost per QALY estimates were within the implied NICE ceiling ratio of £30,000 pounds per QALY gain.

Spinal manipulation: The systematic review of conservative treatment for sciatica identified two RCTs of spinal manipulation. One found that manipulation was more effective than placebo, and another found no difference when compared with manual traction, exercises or corset.[18]

Chemonucleolysis: Chemonucleolysis is a technique that attempts to decrease the volume of a disc herniation by reducing the amount of material contained within the nucleus pulposus by injecting the enzyme chymopapain. A systematic review of lumbar discectomy and percutaneous treatments found three RCTs which compared chymopapain to placebo injection found greater symptom relief in the group that received chymopapain.[26]

Lumbar discectomy: Between 5-15% of patients with lumbar nerve root pain are treated with surgery,[6, 7] usually involving a lumbar discectomy. In the NHS in England in 2005/06 8,683 lumbar discectomies were performed.[22] A Cochrane systematic review of surgery for lumbar disc prolapse [27] found 26 RCTs, but only one RCT comparing discectomy with conservative management. Meta-analyses showed that surgical discectomy produced better clinical outcomes than chemonucleolysis, which is better than placebo. Three RCTs showed no difference in clinical outcomes between microdiscectomy and standard discectomy, but in three other studies, both produced better results than percutaneous discectomy. The review concluded that there was considerable evidence of the clinical effectiveness of discectomy for carefully selected patients with sciatica caused by lumbar disc prolapse that fails to resolve with conservative management. Serious complications from lumbar disc surgery are uncommon with a mortality rate of 0.3%, infection rate of 3% and 4% require an intra-operative transfusion. Surgery fails to relieve symptoms in 10-20% of cases.[26]

Other treatments: There are a number of other treatments that have not been included in previous systematic reviews, for example complementary therapies such as acupuncture. These will be included in the proposed review.

Pattern of treatments: Overall, there is no close correlation between symptom severity and pathology in sciatica. Increasing distance between onset and effective treatment has an unfavourable influence on symptoms and disability. Whilst there is reason to suppose that a stepped care approach to sciatica could be helpful, the application of the various available treatments depends more on availability, clinician preference and socio-economic variables than patient needs. In practice, some patients will recover under an analgesic cocktail whilst on a waiting list, some will be offered surgery as a first line intervention, and yet others will receive a combination of treatments in no particular order. With few exceptions it would appear that the patients attending differing treatment approaches are clinically indistinguishable. This set of issues will be central to the proposed review and synthesis.

3.6 Sources of heterogeneity in studies of sciatica

We anticipate that the review will find a diverse set of studies. Some of the potential sources of heterogeneity includes the following:

Diagnostic heterogeneity: As discussed in the introduction, sciatica is a symptom rather than a strict pathological label. Many of the studies will include patients with referred leg pain as well as nerve root pain. Stricter diagnostic criteria including findings from imaging studies are used more in surgical compared to non-surgical trials. Similarly

when nerve root pain is responsible, causes other than prolapsed intervertebral discs are more likely to be included trials that do not use imaging findings as inclusion criteria.
Treatment group heterogeneity: Different treatments are likely to include different patient groups because of the diagnostic heterogeneity discussed above. Treatments that are further up the gradient of invasiveness, such as disc surgery are more likely to be used in patient populations with fewer cases of referred leg pain, longer duration of symptoms, greater degree of disability and psychosocial morbidity, particularly if patients are receiving treatments in a sequential manner.
Heterogeneity of co-interventions: Co-interventions vary between trials testing the same intervention as well as between different interventions. For example post-operative management after lumbar disc surgery is inconsistent with regard to post-operative restrictions, reactivation, and return to work.[28]
Heterogeneity of health care provision: There is wide variation in the management of sciatica between countries in terms of the use of primary care,[3] the rate of disc surgery[29] and social security provision.[30]
Heterogeneity of outcome measures: The relative importance of the various outcomes (e.g. pain, disability, work status, costs) varies across groups of stakeholders (patients, clinicians, providers) and can change over time, e.g. during the initial stages the patient may value pain relief, but with time functional status may become more important. This will be considered during both review and synthesis.

4. SYSTEMATIC REVIEW METHOD

The review will follow the methodology reported in CRD Report 4.[31] Studies examining effectiveness and those evaluating cost-effectiveness will be reviewed separately.

4.1 Literature search

The following databases will be searched for published, semi-published and grey literature:

- MEDLINE
- MEDLINE in process and other non-indexed citations
- EMBASE
- CINAHL
- PsychINFO
- AMED (Allied and Complimentary Database)
- HMIC (Health Management Information Consortium)
- British Nursing Index
- BIOSIS
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Database of Systematic Reviews
- Health Technology Assessment (HTA) Database
- NHS Economic Evaluation database (NHS EED)
- Science Citation Index
- Social Science Citation Index
- Index to Scientific and Technical proceedings (ISTP)
- System for Information on Grey Literature (SIGLE)
- Inspec
- Physiotherapy Evidence Database (PEDro)

The search strategy for MEDLINE (via OVID) is presented in Appendix 1 and will be translated for use on other databases. No language or date restrictions will be used.

The following trial registries will be searched to identify any further completed or ongoing trials:

- National Research Register (NRR) of ongoing health research (www.doh.gov.uk/research/nrr.htm)
- National Institute for Health's ClinicalTrials.gov database (http://www.clinicaltrials.gov)
- CenterWatch Clinical Trials Listing Service (http://www.CenterWatch.com/)
- Current controlled trials (CCT) (http://www.controlledtrials.com)

The following conference proceedings will be searched by hand where feasible (pending availability) for the last 5 years:

- The European society of Spine
- International society for the study of Spine
- Britspine
- North American society of Spine

The journal Spine will also be searched by hand for the last 5 years

Reference lists of previous systematic reviews and included studies will be screened and citation tracking undertaken where feasible.

The results of the searches will be entered onto the reference management software, Endnote. Articles written in a language other than English will be translated whenever possible. Multiple publication of the same study will be identified, grouped together and represented by a single reference.

4.3 Methods of study selection

4.3.1 Planned inclusion/exclusion criteria

	Clinical effectiveness	***Cost-effectiveness***
Study design	Randomised and non-randomised controlled trials, as well as controlled observational studies.	Economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases will be included if they compare two or more treatments and consider both costs and consequences (including cost-effectiveness, cost-utility, cost-benefit and cost-consequences analysis). Cost-analysis undertaken as part of a comparative study, where data on both costs and consequences are reported, but not combined will also be included.
Patient population	Adults with sciatica or lumbar nerve root pain diagnosed clinically or confirmed by imaging. The essential clinical criterion is leg pain worse than back pain. Other clinical criteria which support the diagnosis include: unilateral leg pain; pain radiation below the knee; aggravated by cough/sneeze; segmental distribution; provocation tests (eg impaired	

	SLR); reduced power, sensation or reflexes in one nerve root. Studies that include participants with low back pain will be included if the findings for patients with sciatica are reported separately; studies where the results are not reported separately for sciatica will be excluded. Studies of specific conditions such as spinal stenosis or discogenic pain will only be included if it is documented that leg pain is worse than back pain. If imaging has been used it must demonstrate evidence of nerve root irritation.	
Interventions	Any	
Comparators	Any placebo, manual, medical, or surgical treatment for sciatica.	
Outcomes	Any relevant patient based outcome measure such as pain, disability, functional status, adverse effects, health status, quality of life, analgesic use, operation rates, health utility, return to work, health service use and costs. Biochemical outcomes and biomechanical measurements (e.g. change in disk space) will be excluded.	Any outcome measure

4.3.2 Assessing relevancy of included studies

Two reviewers will independently screen the titles and abstracts identified by the electronic searches for relevancy. Potentially relevant studies will be ordered and assessed for inclusion, using the criteria reported above, by two independent reviewers. Disagreements during both stages will be resolved by discussion or if necessary taken to a third reviewer.

4.3.3 Further literature needed to inform the economic model

As well as searching for effectiveness and cost-effectiveness studies, we will systematically search for epidemiological studies and case series with long term follow-up data that will inform the economic model. We will also search for studies that identify the type of treatment strategies being used in practice, report prevalence data, provide information on the probability of moving to different states, give estimates of duration in different states, report information on utilities or identify the type of outcome measures that are of importance to patients, clinicians or policy makers. The model will also use resource data from the NHS including costs, tariffs, and unit costs available from national sources.

4.4 Quality assessment

Quality assessment will be undertaken by two independent reviewers with differences being resolved by consensus or by a third reviewer if necessary. Data relating to quality assessment will be inputted on to an Access database.

Effectiveness studies: The quality of included trials and observational studies will be assessed using a checklist based on the one used by the 'Back Review Group' of the Cochrane Collaboration for RCTs[32] and the one developed by the Hamilton Effective Public Health Practice Project (EPHPP) Team for quantitative studies (which includes both comparative observational studies and RCTs) (http://www.myhamilton.ca/myhamilton/CityandGovernment/HealthandSocialServices/Re

search/EPHPP). The checklist is presented in Appendix 1. The criteria cover selection bias and confounding, detection bias, performance bias and attrition bias. Criteria relating to external validity have also been added.

The quality checklist will be used to describe the overall quality of individual studies and the likelihood of bias, and will not be used to calculate an overall quality score. Alternatively the robustness of the quality assessment will be assessed using sensitivity analyses, which will examine the influence of the following individual criteria: randomisation, concealment of allocation, blinding of outcome assessment and loss to follow-up ≤ 80%.

Economic evaluations: The quality of the cost-effectiveness studies will be assessed according to an updated version of the checklist developed by Drummond et al. (Appendix 3).[33] The checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by NICE. For studies based on decision models, the critical appraisal will be based on the checklist developed by Weinstein et al (Appendix 3).[34]

4.5 Data extraction

Data will be extracted using predefined forms developed on a Microsoft Access database. Separate forms will be used for effectiveness studies and cost-effectiveness studies; these will be piloted on a small selection of relevant studies in advance and adjusted if necessary. Multiple publications of the same study will be identified and collated. Data will be extracted by one reviewer and checked against the original paper by a second independent reviewer. Any disagreements will be resolved by discussion or by a third reviewer if necessary.

Data extraction for effectiveness studies (Appendix 4): Study location and setting, description of study population (including method of diagnosis and previous treatment), type of intervention and control used, how allocation was performed, outcome measures used, and results with sufficient information (such as proportions, means, standard deviations, standard errors, significance levels, confidence intervals, numbers needed to treat) to estimate effect sizes wherever possible.

Data extraction for cost-effectiveness studies (Appendix 5): Type of economic evaluation, specific details about the interventions being compared, study population, time period, measures of effectiveness, direct costs (medical and non-medical), productivity costs, resource use, currency, results and details of any decision modelling and sensitivity analysis.

4.6 Methods of analysis/synthesis

Effectiveness studies: The findings will initially be subdivided according to the different treatment modalities. The results of data extraction and quality assessment will be presented in structured tables and also as a narrative summary. Ongoing studies will be reported separately, and the potential impact of their findings will be discussed.

Meta-analysis and meta-regression: This will be conducted for each treatment comparison, for which there are compatible multiple studies, and each outcome measure (including separate analyses for short and long term follow-up). Random effects will be included in the modelling[35] when between-study heterogeneity is present as ascertained by examining (χ^2 and I^2) statistics.[36] The results of these will be presented using forest plots, sub-grouping results by study design. In an attempt to explain any between study heterogeneity, meta-regression will be conducted[37] examining the influence of

characteristics of study design (year, location, randomisation, concealment of allocation, blinding of outcome assessment, >80% follow-up); patient characteristics (mean age, gender proportion); diagnostic heterogeneity (inclusion criteria including physical examination or imaging findings); symptom duration; level of disability and psychosocial morbidity (from baseline measures of health status); failed previous treatment; use of co-interventions. In addition, a sensitivity analysis excluding any non-randomised studies from the analysis will be conducted to assess the influence of the lower quality evidence on the conclusions. For all comparisons for which there are more than 5 studies, funnel plots together with associated tests,[38, 39] will be considered to assess the potential for publication bias.

Mixed Treatment Comparison (MTC): Since it is anticipated that not all treatment comparisons of interest will have been evaluated in controlled studies, we will then synthesise all RCTs which form a closed network[40] using a MTC synthesis methodology.[41] This allows the estimation of all treatment comparisons of interest without breaking within study comparisons and hence randomisation where it exists.[42] Particular care will be taken to ensure treatment regimens are comparable in studies used for the direct and indirect estimation within the model. Informal comparisons between the estimated effects from the individual (direct comparison) meta-analyses and the MTC model will be made, and more formal assessments of the coherence and consistency of the evidence network will be made using deviance information criteria and related statistics[43] as calculated by the Bayesian WinBUGS software.[44] Important covariates, identified from the meta-regression analyses, which explain between study heterogeneity will be included in the MTC model. Novel modelling will also be developed and used to acknowledge issues relating to sequential intervention effects and other specific issues relating to sciatica treatment (for example those listed in Appendix 6). The MTC model will then be further extended by including non-trial data for those comparisons for which there is no available data from RCTs. Information on study quality will be incorporated to take into account the use of data from imperfect sources.[45] It is anticipated that the MTC modelling approach will give estimates of the parameters required for the economic decision model.

Economic evaluations: Details of each published economic evaluation, together with a critical appraisal of its quality will be presented in structured tables and narrative summary. Where appropriate and where the data presented permit, indications of the uncertainty underlying the estimation of the differential cost and effects of the alternative treatment options will be summarised.

Other parameters for the economic evaluation: Previous experience of conducting meta-analyses and associated cost-effectiveness modelling indicates that outcome measures which are of most clinical relevance and interest are not necessarily the outcomes which are most compatible and relevant to the economic model. Therefore, early in the project, those carrying out the evidence synthesis will liaise closely with the decision modelers to ensure syntheses which are required for the decision model are conducted.

In addition to the syntheses to estimate clinical effectiveness, further syntheses may be desirable to estimate other parameters in the economic decision model.[46]

5. COST-EFFECTIVENESS MODELLING

It is likely that the existing evidence relating to the cost-effectiveness of treatments will have a number of limitations which make it insufficient to inform decision-making regarding the most appropriate management strategy for patients with sciatica. Thus it will be necessary to construct an appropriate probabilistic decision analytic model to address a number of these issues more formally. This model will provide a framework for the synthesis of data from the clinical effectiveness, economic reviews and other relevant sources. It will be developed to estimate costs from the perspective of the UK NHS and personal social services[47, 48] and health outcomes in terms of QALYs gained for the range of relevant treatment strategies. (If the findings of the literature review indicate that patients value different outcomes to those of policy makers and clinicians, then the model will be developed using two iterations, including one from the patient perspective.) The number of appropriate and relevant health states will be informed by the results of the service provider survey (see section 5.5 below), the literature review and from advice within the research team. The cost of managing patients within each state will be reflected in the model, while it is not envisaged that patient progression will be seamless, or indeed linear and uni-directional. The structure of the model will reflect this and the probability of movement between health states will be based on the evidence from the literature review, including the distribution around the point estimates. In addition, a sensitivity analysis will be used to assess the impact of 'changes' in the variable estimates, and identify potential areas for future research. A probabilistic sensitivity analysis will assess the extent to which any one particular strategy is likely to be within the bounds of what is considered to be cost-effective.

The model will incorporate a range of time horizons. It is proposed that a probabilistic model be constructed to ensure that uncertainty can be appropriately characterised depending on the range of comparators included in the analysis.[49] Given that mean costs and QALYs gained will therefore be estimated with uncertainty, the outputs from the simulations will be used to generate cost-effectiveness acceptability curves for the alternative analyses. These curves detail the probability that each intervention is cost-effective over a range of potential maximum values that the health service is prepared to pay for an additional QALY.[50] The budgetary impact (again from a NHS perspective) will also be assessed as part of the health economic evaluation.

The findings of the model will be contrasted with other economic evaluations identified by the review, which will also be used to test the inputs and assumptions made in our model.

5.5 Telephone survey of service providers

Approximately 30 service providers known to the advisory group members will be contacted by telephone to determine: their usual clinical practice, the usual treatment pathways and whether they use a stepped care approach. This information will be used to inform which sequence of treatments to include in the economic model.

Previously conducted systematic reviews will be used to generate a list of potential treatments for sciatica. During the telephone interviews clinicians will be asked initially what treatments (including combination and sequence of treatments) they usually use, and afterwards, if prominent treatments identified from previous reviews are not mentioned, they will be asked if they have ever considered using these.

6. RECOMMENDATIONS FOR PRACTICE AND RESEARCH

6.1 Recommendations for practice

We will make recommendations for practice, based on what is feasible within the UK NHS setting. The importance of sequential therapies and a stepped care approach will also be considered with recommendations being made about possible optimum care pathways. We will make comparisons between clinical resolution and return to work.

6.2 Recommendations for further research

The overall findings of the review will be used to make recommendations for further research, including details (such as optimal comparator treatments) of the types of trials which would make important contributions to the existing evidence base.[51] The modelling will inform future research recommendations using 'value of information' (VOI) methods, which equate the cost of further research to the cost of improved decision making that could be done as a result of having the further information. In particular we will use 'expected value of perfect information' (EVPI) to estimate the benefit of having perfect information on all parameters in the model, in order to give an upper bound on the payoff of further information. Additionally, the findings of the quality assessment of the existing comparative studies evaluating treatment effectiveness will be used to make recommendations about how to improve conduct of such studies in the future.

The findings of previous systematic reviews, which are based on conventional meta-analyses, will be compared with ours to see if using the data from observational studies and the additional modelling work results in different conclusions being made.

7. PROJECT TIMETABLE AND MILESTONES

	2008										2009										
Month	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Protocol development																					
Recruit patient representative																					
Search strategy developed and agreed																					
Piloting quality assessment tools																					
Protocol peer review and finalise																					
Literature searching																					
Develop access database and pilot																					
Assessment of relevance and inclusion																					
Write progress report (due in on 1st Sept)																					
Data extraction and quality Assessment																					
Conduct telephone survey of providers																					
Write progress report (due in on 2nd March)																					
Synthesis and analysis of data																					
Economic analysis																					
Report writing																					
Submission of draft final report (due in on 14th Nov)																					

8 PROJECT MANAGEMENT

8.1 Study management

A Study Management Group (SMG) will be formed, and will be responsible for overseeing the progress of the study throughout all of its phases and will meet regularly every one to two months. The day to day management of the study will be co-ordinated through the study co-ordination centre (Wrexham). The reviewing team (Wrexham) and the team conducting the economic evaluation (Swansea) will meet as and when is required by teleconference. A steering committee will be held every three to six months. Data monitoring and quality assurance will be overseen by the steering group.

8.2 Steering Group

The review team as a whole will form a steering group, which will meet every three to six months. The role of the steering group will be to ensure that the study is conducted to a rigorous standard and to make any necessary strategic decisions. Members of the group will also be responsible for approving the protocol and ensuring that the study adheres to it; provide information support (such as answering methodological and clinical queries) to those conducting the review or economic analysis; identify relevant studies that the literature searches may have missed; assist with the analysis and interpretation of the findings; and approve of the final report and any subsequent publications.

9. SERVICE USERS

The review team (steering group) includes a number of service users, which includes clinicians working in the field and a patient representative. The clinicians include general practitioners (NW, CW), osteopaths (NW, KB), a spinal surgeon (IB), and a musculoskeletal physician (RC). The patient representative will be IR who has undergone spinal surgery. A second patient representative who has not undergone surgery will be recruited with the help of the Clinical Research Collaboration Cymru (CRCC) Involving People/Cynnwys Pobl, patient, service user and carer network. Service user representatives will be able to help us ensure the appropriateness of the research question (and inclusion/exclusion criteria), provide input on the type of data to be extracted from primary studies, and provide input on the interpretation of the findings.

9. DISSEMINATION

A final report will be submitted to the funding body. Papers will be submitted to high quality journals and presented at national and international conferences.

10. REFERENCES

1. Deyo RA, Rainville J, Kent DL. What can the history and physical examination tell us about low back pain? *JAMA* 1992;268:760-765.
2. Clinical Standards Advisory Group. *Back pain*. London: HMSO, 1994.
3. Waddell. *The Back pain revolution*. Edinburgh: Churchill Livingstone, 1998.
4. Lawrence JS. *Rheumatism in populations*. London.: Heinemann, 1977.
5. Heliovaara M, Impivaara O, Sievers K, Melkas T, Knekt P, Korpi J, et al. Lumbar disc syndromein [Finland]. *Journal of Epidemiol Community Health* 1987;41:251-258.
6. Bush K, Cowan N, Katz DE, Gishen P. The natural history of sciatica associated with disc pathology; a prospective study with clinical and independent radiological follow-up. *Spine* 1992;18:1433-1438.

7. Weber H, Holme I, Arnlie E. The natural course of acute sciatica with nerve root symptoms in a double blind placebo controlled trial evaluating piroxicam. *Spine* 1993;18:1433-1438.
8. Tubach F, Beaute J, Leclerc A. Natural history and prognostic indicators of sciatica. *Journal of Clinical Epidemiology* 2004;57:174-179.
9. van Tulder MW, Koes BW, Bouter LM. A cost of illness study of back pain in the Netherlands. *Pain* 1995;62:233-240.
10. Mixer WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. *N Engl J Med* 1934;211:210-215.
11. Revdivik B, Brown M, Lundborg G. Pathoanatomy and pathophysiology of nerve root compression. *Spine* 1984;9:7-15.
12. Goupille P, Jayson MI, Valat JP, Freemont AJ. The role of inflammation in disc herniation-associated radiculopathy. *Semin Arthritis Rheum.* 1998;28:60-71.
13. Vroomen PCAJ, M.C.T.F.M. dK, Knotternus JA. Diagnostic value of history and physical examination in patients suspected o sciatica due to disc herniation: a systematic review. *Neurol* 1999;246:899-906.
14. Rebain R, Baxter DG, McDonough S. A systematic review of the passive straight leg raising test as a diagnostic aid for low back pain. *Spine* 2002;27:E388-E395.
15. Agency for Health Care Policy and Research. *Management guidelines for acute low back pain*. Rockville MD: US Department of Health and Human Services, 1994.
16. Hagen KB, Hilde G, Jamtvedt G, Winnem M. Best rest for acute low back pain and sciatica. *The Cochrane Database of Systematic Reviews 2004* 2004.
17. Hagen KB, Hilde G, Jamtvedt G, Winnem M. Advice to stay active as a single treatment for acute low back pain and sciatica. *The Cochrane Database of Systematic Reviews 2004* 2004.
18. Vroomen PCAJ, de Krom MCTFM, Slofstra PD, Knotternus JA. Conservative treatment of sciatica: a systematis revies. *Spinal Disorders* 2000;13:463-469.
19. Li LC, Bombardier C. Physical therapy management of low back pain: an exploratory survey of therapist approaches. *Physical Therapy* 2001;81:1018-1028.
20. Harte AA, Gracey JH, Baxter GD. Current use of lumbar traction in the management of low back pain: results of a survey of physiotherapists in the United Kingdom. *Arch Phys Med Rehabil* 2005;86:1164-1169.
21. Clarke JA, van Tulder MW, Blomberg SEI, de Vet HCW, van der Heijden GJMG, Brinfort G. Traction for low back pain with or without sciatica. *The Cochrane Database of Systematic Reviews 2005* 2005.
22. Hospital Episode Statistics. 2007. Available from: http://www.hesonline.nhs.uk. [cited 25 January 2007]
23. Koes BW, Scholten RJPM, Mens JMA, Bouter LM. Efficacy of epidural steroid injections for low back pain and sciatica: a systematic review of randomized control trials. *Pain* 1995;63:279-288.
24. DePalma MJ, Bhagava A, Slipman CW. A critical appraisal of the evidence for selective nerve root injection in the treatment of lumbosacral radiculopathy. *Arch Phys Med Rehabil* 2005;86:1477-1483.
25. Price C, Arden N, Coglan L, Rogers P. Cost-effectiveness and safety of epidural steroids in the management of sciatica. *Health Technology Assessment* 2005;9.
26. Stevens CD, Dubois RW, Larequi-Lauber T, Vader J-P. Efficacy of lumbar discectomy and percutaneous treatments for lumbar disc herniation. *Soz Praventivmed* 1997;42:367-379.
27. Gibson JNA, Grant IC, Waddell G. The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. *Spine* 1999;24:1820-1832.

28. McGregor AHB, A. K. Sell, P. Waddell, G. The development of an evidence based patient booklet for patients undergoing lumbar discectomy and un-instrumented decompression. *European Spine Journal* 2006;DOI: 10.1007/s00586-006-0141-9.
29. Cherkin DC, Deyo RA, Loeser JD, Bush T, Waddell G. An international comparison of back surgery rates. *Spine* 1994;19:1201-1206.
30. Waddell GN, A. I. Review of social security systems. In: Nachemson AL, Jonsson E, editors. *Neck and back pain*. Philadelphia: Lippincott Williams & Wilkins, 2000. p. 427-471.
31. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews*. 2nd ed. York: NHS CRD, University of York, 2001.
32. van Tulder MW, Furlan A, Bombardier C, Bouter LM, Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. *Spine* 2003;28:1290-1299.
33. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press, 2005.
34. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices-Modeling Studies. *Value in Health* 2003;6:9-17.
35. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. *Methods for meta-analysis in medical researched*. London: John Wiley, 2000.
36. Higgins JPT, Thompson SG, Deeks JD, Altman DG. Education and debate: Measuring inconsistency in meta-analysis. *BMJ* 3003;327:557-560.
37. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Statistics in Medicine* 1999;18:2693-708.
38. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634.
39. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;295:676-80.
40. Lumley T. Network meta-analysis for indirect treatment comparisons. *Statistics in Medicine* 2002;21:2313-24.
41. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine* 2004;3105-24:3105-24.
42. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331:897-900.
43. Spiegelhalter DJ, Best NG, Carlin BR, van der Linde A. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society Series B* 2002;64:583-616.
44. Spiegelhalter DJ, Thomas A, Best NG. *WinBUGS Version 1.4. User manual*. Cambridge: MRC Biostatistics Unit, 2000.
45. Turner RM, Spiegelhalter DJ, Smith GCS, Thompson SG. Bias modelling in evidence synthesis. *Journal of the Royal Statistical Society Series A (In Press)*.
46. Cooper NJ, Sutton AJ, Abrams KR, Turner D, Waioloo A. Comprehensive decision analytical modelling in economic evaluation: A Bayesian approach. *Health Economics* 2004;13:203-26.
47. Curtis L, Netten A. *Unit Costs of Health and Social Care*. PSSRU University of Kent, 2006. Available from: http://www.pssru.ac.uk/pdf/uc/uc2006/uc2006.pdf. [cited 29/01/07]
48. Department of Health. *NHS Reference Costs 2005-06*. Available from: http://www.dh.gov.uk/assetRoot/04/14/14/30/04141430.xls. [cited 29/01/07]

49. Briggs AH. Handling uncertainty in economic evaluation and presenting the results. In: Drummond MF, McGuire A, editors. *Economic evaluation in health care: merging theory with practice*. Oxford: Oxford University Press, 2001.
50. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Economics* 2001;10:779-87.
51. Sutton AJ, Cooper NJ, Jones DR, Lambert PC, Thompson JR, Abrams KR. Evidence-based sample size calculations based upon updated meta-analysis. *Statistics in Medicine* 2006;(In press& available on early view).
52. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervetnion studies. *Health Technolology Assessment* 2003;7.

APPENDIX 1: Search strategy

The following search strategy was developed for MEDLINE using the Ovid interface. This will be translated for use on other databases.

1. Sciatica/
2. (ischialg$ or sciatic$).ti,ab.
3. ((lumb$ or sacra$ or spin$) adj5 radicul$).ti,ab.
4. ((sciatic nerve or lumbar nerve or spinal nerve or sacral nerve) adj5 (irritation or inflammat$ or pain or neuropath$ or dysfunction$ or compressio$ or injur$ or traum$)).ti,ab
5. Intervertebral Disk Displacement/
6. ((intervertebral disk or intervertebral disc or lumbar disc or lumbar disk or lumbosacral disc or lumbosacral disk or lumbo-sacral disc or lumbo-sacral disk) adj5 (hernia$ or slip$ or prolapse or degeneration or fusion or sclerosis or rupture or distortion or fracture or displacement)).ti,ab.
7. ((lumbosacral nerve root or lumbo-sacral nerve root or lumbar nerve root) adj5 (irritat$ or inflammat$ or pain$ or neuropath$ or dysfunction$ or compressio$ or injur$ or traum$)).ti,ab.
8. ((refer$ or radiat$) adj5 (back or leg or foot)).ti,ab.
9. or/1-8
10. (treatment$ or therap$ or manag$ or surg$ or modalit$ or intervention$).ti,ab.
11. Bed rest/
12. (bed rest$ or activ$ or exercise$ or education$ or instruction$ or advice$).ti,ab.
13. Physical Therapy Modalities/
14. ((heat or hot or thermal or infra?red or ultrasound or ultrasonic or short-wave or physio$ or physical or exercise) adj5 (therap$ or treatm$)).ti,ab.
15. Transcutaneous Electric Nerve Stimulation/
16. (transcutaneous electric nerve stimulation or TENS).ti,ab.
17. Complementary Therapies/
18. Exp Musculoskeletal Manipulations/
19. Exp Acupuncture Therapy/
20. ((spina$ or chiropract$ or osteopath$ or physi$ or homeopath$ or acupunctur$ or musculo?skeletal or myofunctional) adj5 (massage or manipulat$ or therap$ or treatment$)).ti,ab.
21. Homeopathy/
22. homeopathy.ti,ab.
23. Herbal Medicine/
24. herbal medicine.ti,ab.
25. Orthotic Devices/
26. (braces or slings or splints or corset).ti,ab.
27. Traction/
28. traction.ti,ab.
29. Drug Therapy/
30. Exp Analgesics/
31. Anti-Inflammatory Agents, Non-Steroidal/
32. ((non-steroidal anti inflammatory or non-steroidal anti-inflammatory or non?narcotic or narcotic or opioid$ or opiate$) adj5 (drug$ or analges$)).ti,ab.
33. (paracetamol or acetaminophen).ti,ab.
34. (ibuprofen or aceclofenac or acemetacin or celecoxib or dexketoprofen or diclofenac sodium or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or indometacin or indomethacin or ketoprofen or mefenamic acid or

meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid or azapropazone or biarison or acetaminophen or nimesulide or oxyphenbutazone or azapropazone or felbinac or alclofenac or nimesulid or etofenama or loxoprofen or phenylbutazone or valdecoxib or lornoxicam or etoricoxib).ti,ab.

35. (buprenorphine or butorphanol or codeine or dextromoramide or dextropropoxyphene or dihydromorphine or diphenoxylate or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or levorphanol or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or tilidine or tramadol).ti,ab.
36. Epidural Analgesia/
37. Epidural Injections/
38. ((intramuscular or intravenous or peri?neural$ or epidura$ or inject$) adj5 (cortico?steroid$ or steroid$ or ana?lgesic$ or chymopapain)).ti,ab.
39. (dexamethasone or hydrocortisone or prednisolone or methylprednisolone or prednisone or methylprednisone or triamcinolone).ti,ab.
40. Orthopedic Procedures/
41. Intervertebral Disk Chemolysis/
42. ((disc or disk) adj5 (chemolysis or chemonucleolysis)).ti,ab.
43. Vertebroplasty/
44. Diskectomy/
45. Neurosurgical Procedures/
46. Laminectomy/
47. Rhizotomy/
48. (discectomy or diskectomy or microdiscectomy or microdiskectomy or rhizotomy or sequestrectomy or vertebroplasty or nucleoplasty or laminectomy).ti,ab.
49. Surgical Decompression/
50. surgical decompression.ti,ab.
51. or/11-50
52. 9 and 51
53. limit 52 to humans

APPENDIX 2: Quality assessment for effectiveness studies

Controlled trials and observational studies will be assessed using the following criteria, which are based on the checklist reported by van Tulder et al,[32] and the one developed by The Effective Public Health Practice Project (EPHPP) Team (http://www.myhamilton.ca/myhamilton/CityandGovernment/HealthandSocialServices/Research/EPHPP).

The definition for selection bias used by EPHPP relates to the study sample not being representative of the target population. However, here we have used the term selection bias in relation to the systematic difference between the comparison groups at baseline.

EXTERNAL VALIDITY

Are the individuals selected to participate in the study likely to be representative of the target population?

In order to receive a YES, authors must have done everything reasonably possible to ensure that the target population is represented. The study will be scored PARTIAL if participants might not be representative, e.g. if they were referred from a specific source (a single GP practice or clinic etc.) within a target population even if it is in a systematic manner. The study will be scored NO if patients are self-referred.

What percentage of selected individuals agreed to participate?

(80-100%, 60-79%, <60%) The % of subjects in the control and intervention groups that agreed to participate in the study before they were assigned to intervention or control groups. This item will be graded as NA if the study was directed at a group of people in a specific geographical area, city…etc.

Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

The reviewer will determine if this is adequate or enough information is given in order to score YES.

SELECTION BIAS & CONFOUNDERS

Study Design

Studies will be categorised using the taxonomy reported by Deeks et al.[52] (which has been adapted from CRD report 4[31]).

Was the method of randomisation adequate?

The method of random allocation is adequate if the randomisation sequence allows each study participant to have an equal chance of receiving each intervention, e.g. computer generated random numbers and random number tables. The method of random allocation is deemed inadequate (and scored NO) if it is not entirely transparent, e.g. the method of randomisation is described as alternation, case record numbers, dates of birth, day of the week. Studies that use serially numbered envelopes, with no further information about how the random number sequence was generated will be scored as UNCLEAR. Studies that just use the term 'randomisation' or 'random allocation' will be scored as UNCLEAR. Non-randomised studies would score NO.

Was the treatment allocation concealed?

In order to receive a YES, the person recruiting and assessing the eligibility of participants should have no information or influence on assignment of the intervention, and they should not be able to predict allocation. Ideally, allocation should be remote or secure from all clinicians. Examples of adequate approaches include centralised or pharmacy-controlled randomisation, and on-site computer based system with randomisation sequence that is not readable until allocation. The reviewer will score

studies that use serially numbered identical containers, serially or sequentially numbered envelopes, or opaque sealed envelopes as PARTIAL. Examples of inadequate approaches include alteration, case record numbers, week days, open random number lists. Observational studies would score NO.

Indicate the percentage of relevant prognostic factors that were measured in both groups prior to the intervention.

*(*80-100%, 60-79%, <60%). *Relevant prognostic factors relate to: demographic factors, socioeconomic factors, duration & severity of sciatica, psychological factors, previous treatments, past medical history, physical factors (e.g. straight leg raise test), and value of main outcomes.*

Were the groups similar at baseline for relevant prognostic factors?

The reviewer will determine if this is adequate or enough information is given in order to score YES.

Were all participants recruited from same population (or appropriate alternative)?

The reviewer will determine if this is adequate or enough information is given in order to score YES.

Were participants in both groups recruited over the same time (or similar point in their disease/illness/treatment?)

The reviewer will determine if this is adequate or enough information is given in order to score YES.

Was an analysis of covariance (ANCOVA) or similar method used to allow for possible baseline imbalance?

In order to receive a YES the study should use a method of analysis that controls for possible baseline imbalance between groups. If differences between groups for important confounders have been controlled for in the design (stratification or matching) then the study should also be marked as YES.

Were co-interventions avoided or similar?

In order to score YES, co-interventions should either be avoided in the trial design or similar between the intervention and control groups.

DETECTION BIAS

Accuracy of data collection tool:

a- Were tools shown to be valid?

The item will receive a YES if the tools are known or have been shown to measure what they were intended to measure, and NO if there was no attempt to show that the tools measured what they were intended to measure. Tools that are unreferenced are unlikely to been validated. Where the primary outcomes are reported, these are the outcomes measures which will be used to assess this criterion.

b- Were tools shown to be reliable?

The item will receive a YES if the tools are known or have been shown to be consistent and accurate in measuring the outcome of interest (e.g., test-retest, Cronback's alpha, interrater reliability), and NO if there was no attempt to show that the tools were consistent and accurate in measuring the outcome of interest. Tools that are unreferenced are unlikely to been tested for reliability.

Was the timing of outcome assessment in all groups similar?

In order to score YES, the timing of outcome assessment should be identical for all intervention groups and for all important outcomes assessments.

Were the outcome assessors blinded to the intervention or exposure status of participants?

The study will be scored YES if the assessors were described as blinded to which participants were in the control and intervention groups, and NO if the assessors were

able to determine what group the participants were in. The study will be scored NA if the data were self-reported and collected by way of a survey, questionnaire or interview.
Were data analysts blinded to participants groups?
The study will be scored YES if the analysts were described as being blind to which participants were in the control and intervention groups, and NO if the analysts were able to determine which group the participants were in.
[Studies that fail this last criterion will only receive a 'moderate' or 'weak' for performance bias.]

PERORMANCE BIAS
Were the participants blinded to the intervention?
The reviewer will need to determine if this is adequate or enough information about the blinding is given in order to score 'YES'. Studies marked as 'double blind' with no further information will be marked as PARTIAL.
Were the physicians blinded to participants groups?
The reviewer will need to determine if this is adequate or enough information about the blinding is given in order to score 'YES'. Studies marked as 'double blind' with no further information will be marked as PARTIAL.
Were there any attempts to test the efficacy of blinding procedures?
The reviewer will need to determine if this is adequate or enough information is given in order to score YES.

ATTRITION BIAS
Were the characteristics of drop-outs similar to those who remained in the study?
The reviewer will need to determine if this is adequate or enough information is given in order to score YES. Studies with ≤5% dropouts will receive a YES.
Was there a differential drop-out rate between the groups?
The reviewer will need to determine if this is adequate or enough information is given in order to score YES.
Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest
(80-100%, 60-79%, < 60%). *The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term (*≤ 3 mths*) or medium-term (*3-11 mths*) follow-up and 30% for long-term (*≥12 mths*) follow-up and does not lead to substantial bias, a YES is scored. (N.B. these percentages are arbitrary, not supported by literature.)*
Is the analysis performed according to intervention allocation status rather than actual intervention received?
The reviewer will need to determine if this is adequate or enough information is given in order to score YES.
Did the analysis include all allocated patients irrespective of non-compliance?
The reviewer will need to determine if this is adequate or enough information is given in order to score YES. Studies with ≤5% dropouts will receive a YES.

Items will be graded as either **YES** (+), **NO** (-), **Partial** (+/-), **Unclear** (or not enough information or not stated) and **NA** not applicable

APPENDIX 3: Quality assessment for economic evaluations

All Studies of cost-effectiveness will be assessed using the same checklist and decision analysis will be evaluated using an additional checklist.

Economic evaluations will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond and colleagues:[33]

Study question

1. Costs and effects are examined.
2. Alternatives are compared.
3. The viewpoint(s)/perspective of the analysis is clearly stated (*e.g. NHS, society*).

Selection of alternatives

4. All relevant alternatives are compared (*including do nothing if applicable*)
5. The alternatives being compared are clearly described (*who did what, to whom, where and how often*).
6. The rationale for choosing the alternative programmes or interventions compared is stated.

Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, equivalent outcomes are adequately demonstrated.

Effectiveness data

9. The source(s) of effectiveness estimates are stated (*e.g. single study, selection of studies, systematic review, expert opinion*)
10. Effectiveness data from a RCT or review of RCTs.
11. Potential biases identified (especially if data not from a RCT).
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).

Costs

13. All the important and relevant resource use is included.
14. All the important and relevant resource use is measured accurately (with methodology).
15. Appropriate unit costs are estimated (with methodology).
16. Unit costs are reported separately from resource use data.
17. Productivity costs are treated separately from other costs.
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.

Benefit measurement and evaluation

19. The primary outcome measure(s) for the economic evaluation are clearly stated (*cases detected, life-years, QALYs, etc.)*.
20. Methods to value health states and other benefits are stated (*e.g. time trade-off*).
21. Details of the individuals from whom valuations were obtained are given (*patients/members of the public/healthcare professionals).*

Decision modelling

22. Details of any decision model used are given (*e.g. decision tree, Markov model*).
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified.
24. All model outputs are described adequately.

Discounting

25. A discount rate is used for both costs and benefits.
26. The discount rates accord with NHS guidelines (3.5% for costs and benefits and adjusted to 0% and 6% in sensitivity analysis).

Allowance for uncertainty

Stochastic analysis of patient-level data

27. Details of statistical tests and CIs are given for stochastic data.
28. Uncertainty around cost-effectiveness is expressed (*e.g. CI around ICER, cost-effectiveness acceptability curves*).
29. Sensitivity analysis is used to assess uncertainty in non-stochastic variables (*e.g. unit costs, discount rates*) and analytic decisions (*e.g. methods to handle missing data*).

Stochastic analysis of decision models

30. All appropriate input parameters are included with uncertainty.
31. Second-order uncertainty (uncertainty in means) is included rather than first-order uncertainty (uncertainty between patients).
32. Probability distributions are adequately detailed and appropriate.
33. Sensitivity analysis is used to assess uncertainty in non-stochastic variables (*e.g. unit costs, discount rates*) and analytic decisions (*e.g. methods to handle missing data*).

Deterministic analysis

34. The approach to sensitivity analysis is given (*e.g. univariate, threshold analysis*).
35. The choice of variables for sensitivity analysis is justified.
36. The ranges over which the variables are varied are stated.

Presentation of results

37. Incremental analysis is reported using appropriate decision rules.
38. Major outcomes are presented in a disaggregated as well as an aggregated form.
39. Applicable to the NHS setting.

Items will be graded as either **YES** (+ *item adequately addressed*), **NO** (- *item not adequately addressed*), **Partial** (+/-), **Unclear** (or not enough information or not stated) and **NA** not applicable

Studies that incorporate a decision analytical model will be furtherer evaluated using the following criteria based on work of Weinstein et al.:[34]

Decision Context

(1) Is there a full description of the decision question, its context, and the process by which this was identified?
(2) Do the model structure & parameters adequately represent the key decision options and perspective?
(3) Do the treatment options cover those of immediate interest to the decision maker?
(4) Are there additional treatment options likely to be of interest in other decision and clinical contexts?
(5) Is the model structure easily adaptable to include future developments?

Health States and Clinical Outcomes

(1) Does the model structure fit (appropriate & relevant) with the clinical theory of the disease process?
(2) Does the model appropriately capture the full impact and cost of treatments?
(3) Does the model appropriately represent the patient population(s) of concern?
(4) How has heterogeneity been included in the model?
(5) Were appropriate methods used to include patients' treatment and disease history and effects on event rates?
(6) Does the model clearly list and justify structural assumptions, and likely impacts on outcomes?
(7) How were structural aspects tested by the modeller (e.g. clinical opinion, literature review, clinical guidelines)?
(8) Was the modelling methodology fully justified (e.g. Markov, decision tree, discrete simulation)?

Transparency

(1) Is the model structure transparent (structure, parameters and values)?
(2) Is the physical model fully accessible to a non-modelling audience?

Timing

(1) Are time horizons appropriate, given the disease, treatments and decision context (1-year, 10-year, lifetime)?
(2) Are the model's cycle times appropriate to the disease and treatments of interest?
(3) Have appropriate methods been used to extrapolate data over extended time horizons?

Data values

(1) Is there a full description of a thorough review process identifying data values?
(2) Are the sources of data values fully described and appropriate?
(3) Are there clear criteria for data inclusion / exclusion?
(4) Are there appropriately documented value ranges for data parameters for sensitivity analysis?
(5) Is there clear identification of areas in the model populated with clinical opinion? Is the approach appropriate?

Data preparation

(1) Are there full details on data preparation to generate parameter values (e.g. meta-analysis, relative risk rates, estimation of utility, calculation of transition rates)?

(2) Were transition rates correctly calculated from interval data?
(3) Were survival data appropriately extrapolated / modelled (e.g. weibull, exponential)?
(4) Are sensitivity analysis adequately handled and classified (e.g. probabilistic, one way, multi-way)?

Data incorporation
(1) Are data units, time intervals and patient characteristics consistent?
(2) Was uncertainty adequately incorporated in the model using appropriate sensitivity structures and analyses?

Internal validation
(1) Was there a thorough and adequate quality control / error checking test plan?
(2) Was the model replicated and compared using alternative software?
(3) Was there a clinical face-value reality check? How was this conducted (e.g. internal review, expert review)?
(4) Was the model shown to accurately replicate data used in model construction?

Cross-model validation
(1) Was the model directly compared and contrasted with existing models in the same disease area?
(2) Were differences between models appropriately discussed, categorized and acted on?

External validation
(1) Was the model validated against independent data?
(2) Were data suitable in terms of its context for comparison (patient group, treatments, timelines, outcomes)?
(3) Which interim outputs were matched?

Items will be graded as either **YES** (+ *item adequately addressed*), **NO** (- *item not adequately addressed*), **Partial** (+/-), **Unclear** (or not enough information or not stated) and **NA** not applicable

APPENDIX 4: Data extraction for effectiveness studies

Data will be extracted into an Access form under the following headings. Separate forms will be used for study details and results.

[] Indicates a list of options included in a pull down box
() indicates a click on/off button, where *on* represents 'yes' and *off* 'no'
{} indicates free text entered in a box

STUDY DETAILS

Reviewer [RL, NW, HM, ND, MH]
Author
Year of publication
EndNote ref. no {i.e. # no.}
Country of origin
Study design [RCT, quasi-RCT, CCT, cohort study, case-control study, before/after study, others]
Setting [hospital, non-hospital or community, other]
Study duration [short term ≤ 3 mths, medium term 3 mths-1 yr, long term ≥1 yr]

STUDY PARTICIPANTS

Population Characteristics {describe population characteristics including age, gender,…etc}
Diagnosis details [Clinical, confirmed by imaging], {describe method of diagnosis and criteria used}
Sciatica type [Nerve root pain, Nerve root pain & refereed pain]
Mixed study [Sciatica *(leg pain only)*, Sciatica and back pain *(including those without sciatica such as back pain but no leg pain)*]
Duration of symptoms {}
Previous treatment [Analgesia/NASIDS, Injections including Epidural, Physical treatment including Traction and Manipulation, Chemonucleolysis, Disc surgery, other], {}
Exclusion Criteria {}
No, eligible patients included {}

INTERVENTION/CONTROL

Type of intervention [Analgesia/NASIDS, Injections including Epidural, Physical treatment including Traction and Manipulation, Chemonucleolysis, Disc surgery, other], {}
Intervention 1 {description including components, technique, dosage, timing therapist experience}
No. patients randomised to intervention 1
No. patients completed the study in the intervention 1 group
Intervention 2 {description including components, technique, dosage, timing therapist experience}
No. patients randomised to intervention 2
No. patients completed the study in the intervention 2 group
Intervention 3 {description including components, technique, dosage, timing therapist experience}
No. patients randomised to intervention 3
No. patients completed the study in the intervention 3 group
Intervention 4 {description including components, technique, dosage, timing therapist experience}

No. patients randomised to intervention 4
No. patients completed the study in the intervention 4 group
Control Group {description including components, technique, dosage, timing therapist experience}
No. patients randomised to control group
No. patients completed the study in the control group

OUTCOME MESUARES
Primary outcome {including the scale if stated}
Secondary outcome {including the scale if stated}

COMMENTS {}

RESULTS

Outcomes will be categorised under:

- General – e.g. overall improvement, satisfaction with treatment
- Pain
- Function
- Well-being – including HRQL, psychological well-being
- Disability
- Side-effects
- Cost
- Resource use
- Qualitative

APPENDIX 5: Data extraction for economic evaluations

Data will be extracted into an Access form under the following headings.

[] Indicates a list of options included in a pull down box
() indicates a click on/off button, where *on* represents 'yes' and *off* 'no'
{} indicates free text entered in a box

Endnote reference number {# no.}
Author {i.e. Jones et al}
Year {i.e. Year of publication or date of interim data collection}
Type of economic evaluation [cost-analysis, cost effectiveness analysis, cost utility analysis, cost-minimisation, cost benefit analysis]
Currency used [$US, £Sterling……...,not stated]
Year to which costs apply {Enter year or not stated}
Perspective used {e.g. health service, societal, hospital, third party payer, patient, unclear}
Study population {describe the population characteristics}
Intervention 1 {description of intervention 1}
Intervention 2 {description of intervention 2}
Control {description of control}
Source of effectiveness data [single study, review/synthesis of previous studies, expert opinion, not stated]
Source of resource use data [single study, review/synthesis of previous studies, expert opinion, not stated]
Source of unit cost data [literature, data from actual source, combination of literature and data from actual source, not stated]
Link between cost and effectiveness data [prospective/concurrent, retrospective/disconnected…]
Clinical outcomes measured and methods of valuation used {summary of outcomes and valuation methods used}
Should we list the costs and resources used, were possible?
Direct costs {medical and non-medical}
Productivity costs {}
Resource use {}
Estimation of costs
Cost data handled appropriately {summary of methods used to e.g. discount, inflate}
Modelling {summary of models used, type of model, purpose of model, components of model, key input parameters and model outputs}
Outcome measures used in economic evaluation {summary of outcome measures used in economic evaluations e.g. incremental cost-effectiveness ratio, net benefit, cost-effectiveness acceptability curve}
Direction of result with appropriate quadrant location
Statistical analysis for patient-level stochastic data {summary of analyses used}
Appropriateness of statistical analysis {comment on appropriateness}
Uncertainty around cost-effectiveness expressed
Appropriateness of method of dealing with uncertainty around cost-effectiveness
Sensitivity analysis {list summary of analysis}
Appropriateness of sensitivity analysis {comment on appropriateness}
Modelling inputs and techniques appropriate
Author's conclusions {list as in publication}

Implications for practice {summary of implications}
Comments {summary of comments}

APPENDIX 6: Specific issues or problems identified for reviewing the evidence relating to sciatica treatment

1. The method (and criteria) used for diagnosing sciatica, and therefore the patient population, are likely to differ according to the invasiveness of the treatment. Strict criteria to diagnose sciatica may not be used for less invasive conservative treatments, and the patient population is likely to include patients with lumbar nerve root pain and referred leg pain, where as imaging techniques (to identify patients with lumbar nerve root pain) are more likely to be used to select patients for more invasive treatments such as surgery. Patients receiving invasive treatments are also more likely to have longer duration of symptoms, but this is not necessarily always the case. This means that the prognosis or baseline risk of the study population is likely to differ (inconsistently) for different interventions.
2. There is no close correlation between symptom severity and pathology in sciatica, and an increasing distance between symptom onset and effective treatment has an unfavourable influence on symptoms and disability. This means that using severity of symptoms to dictate the sequence of invasiveness of treatment modalities in a step wise approach may not always be appropriate. In addition, identifying patients who are unlikely to respond to treatment will be difficult.
3. In clinical practice, the application of various treatment modalities is dependant on availability, clinician preference, and socio-economic factors rather than patient needs. This means that the sequence of treatment modalities used in RCTs and observational studies will differ.
4. There are an infinite number of treatment sequences (but likely to be a finite number of usual routes used in clinical practice), not all of which will have been evaluated in RCTs or considered in observational studies even though they may be effective.
5. Different treatment modalities may interact to produce additional therapeutic benefit that may not be achieved if used on their own. The effect of this interaction will differ according to the sequence of treatments, the time interval between treatments, and responsiveness of the patient.
6. Co-interventions will not be used in the same way for different treatment modalities. Different countries appear to have a different preference for various treatment modalities, as well as the use of co-interventions.
7. RCTs are more likely to evaluate treatment given in isolation, rather than as part of a sequential step-wise approach. However, the data from RCTs of individual therapies may not be comparable. Different treatment modalities of different level of invasiveness are likely to be evaluated using different duration of follow-up and outcome measures.
8. Even if RCTs evaluate 2nd line or subsequent therapy (or alternatively recruit patients with refractory disease), the data they provide on sequential treatment options may be limited. The type and sequence of treatment previously tried by patients are likely to differ considerably.
9. Some treatment modalities are complex interventions, whilst others such as drug therapy are simpler.