Cost-effectiveness of different strategies to manage patients with sciatica

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Summary

A model-based economic evaluation demonstrates that stepped approaches based on initial treatment with non-opioids are most likely to represent the most cost-effective regimens for sciatica.

Abstract

The aim of this paper is to estimate the relative cost-effectiveness of treatment regimens for managing patients with sciatica**.** A deterministic model structure was constructed, based on information from the findings from a systematic review of clinical and cost-effectiveness, published sources of unit costs and expert opinion. The assumption was patients presenting with sciatica would be managed through one of three pathways (primary care, stepped approach, immediate referral to surgery).. Results were expressed as incremental cost per patient with symptoms successfully resolved. Analysis also included incremental cost per utility gained over a 12 month period. One-way sensitivity analyses were used to address uncertainty. The model demonstrated that none of the strategies resulted in 100% success. For initial treatments, the most successful regime in the first pathway was non-opioids, with a probability of success of 0.613. In the second pathway, the most successful strategy was non-opioids, followed by biological agents, followed by epidural/nerve block and disc surgery, with a probability of success of 0.996. Pathway 3 (immediate surgery) was not cost-effective. Sensitivity analyses identified that the use of the highest cost estimates results in a similar overall picture. While the estimates of cost per QALY are higher, the economic model demonstrated that stepped approaches based on initial treatment with non-opioids are likely to represent the most cost-effective regimens for the treatment of sciatica. However, development of alternative economic modelling approaches is required.

Introduction

Understanding the clinical and cost-effectiveness of different management strategies for sciatica is important in order to prevent patients with acute or sub-acute symptoms developing a more chronic condition that is resistant to treatment and likely to incur high healthcare, socio-economic costs and impact on patient outcomes. It is well accepted that taking into account value for money is important in health care decision making. This requires formal assessments of best available evidence on cost-effectiveness, and where necessary, undertaking economic modelling studies if there is a lack of good quality evidence.

Within the United Kingdom (UK), the prevalence of sciatica has been reported as 3.1% in men and 1.3% in women [1], accounting for less than 5% of lower back pain cases presenting in primary care [2]. A large population study based in Finland found a lifetime prevalence of 5.3% in men and 3.7% in women [3]. Some cohort studies have reported that most patients will have a resolution of their sciatica over a period of weeks to months, with 30% having persistent, troublesome symptoms at one year with 20% out of work and 5-15% requiring surgery [4,5]. However, another cohort study 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 by four years) [6]. As the sciatica becomes chronic (>12 weeks), or with recurrent episodes, it becomes less responsive to treatment [7]. The cost of sciatica to society in the Netherlands in 1991 was estimated at United States (US) $ 128 million for hospital care, US$730 million for absenteeism and US$ 708 for disablement [8]. According to 2013 prices, these would be US$219,490,000 (£136,524,000 US$, 125,178,000 (£778,614,000) and US$ 1,214,056,000 (£755,149,000) respectively..

There is no agreed clinical definition for sciatica, and it is commonly considered a symptom rather than a disease. It is characterised as being distinguishable from non-specific low back pain by specific clinical features. These include a 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 usually radiates to the foot or ankle. It is often associated with numbness or paraesthesia in the same distribution [9,10].

A variety of surgical and non-surgical treatments have been used to treat sciatica, with systematic reviews finding evidence for the clinical effectiveness of invasive treatments such as epidural steroid injection, chemonucleolysis and lumbar discectomy in the treatment of sciatica, but found

insufficient evidence for less invasive treatments such as bed rest and analgesia. No indirect comparisons across separate trials were made or examination of cost-effectiveness [11].

Based on the findings of a systematic review of both clinical and cost-effectiveness [11], the aim of this paper is to estimate the relative cost-effectiveness of different treatment regimens for managing patients with sciatica. A further aim is to inform future economic modelling approaches to assess the relative cost-effectiveness of treatment regimes for sciatica.

Methods

Secondary research methods were used to undertake a model-based economic evaluation. The first stage utilised the results of a systematic review to synthesise estimates of clinical effects. The second stage involved the construction of the model, followed by evaluation of the base-case and testing the robustness of the base case findings to changes in assumptions in the data through sensitivity analyses.

Systematic review

A systematic review was undertaken according to the methodology reported in the Centre for Reviews and Dissemination (CRD) report [12] and the Cochrane handbook for systematic reviews of interventions [13]. Studies examining clinical effectiveness and those evaluating cost-effectiveness were reviewed separately.

Major electronic databases (e.g. MEDLINE) and several internet sites including trial registries (e.g. Cochrane Central Register of Controlled Trials (CENTRAL)were searched from inception up to December 2009. Any comparative study or full economic evaluation was considered for inclusion. Studies involving adults who had sciatica or lumbar nerve root pain diagnosed clinically or confirmed by imaging were eligible; with a requirement for leg pain to be worse than back pain. To ensure consistency, this population also formed the basis for the economic model. Studies that included participants with lower back pain were included only if the findings for patients with sciatica were reported separately. Any intervention or comparator used to treat sciatica was included. Data were extracted by one reviewer and checked by a second reviewer. Quality assessment was conducted independently by two reviewers. Disagreements [8 papers were queried for the health economics review] were resolved by discussion and, when necessary, a third reviewer was consulted.

For the review of clinical effectiveness, interventions were grouped into 18 treatment categories (see table 1). Pair-wise (standard) meta-analyses were initially conducted followed by mixed treatment comparison (MTC) analysis. Analysis considered three main outcomes: global effect (including absence of pain), reduction in pain intensity (measured using a continuous scale) and improvement in function based on a composite condition-specific outcome measure (CSOM) as continuous data using weighted mean difference and standardised mean difference, respectively.

Missing study-level outcome data, where feasible, were dealt with by inputting replacement values from published data such as standard deviations standard methods, such as standard deviations (SDs) derived from standard errors (SEs) [13]. Where mean values were unavailable but medians were reported, these were used instead. If SDs for baseline values were available, these were substituted for missing SDs. For studies that did not report sufficient data to derive the SDs, they were imputed using the weighted mean [14], which was calculated separately for each intervention category. For the pair-wise analysis, the data were analysed according to three follow-up intervals: short (≤ 6 weeks), medium (> 6 weeks to 6 months) and long term (> 6 months).

MTC meta-analyses were carried out to enable the simultaneous comparison of all treatment modalities for sciatica at a single follow-up interval (closest to 6 months). The analyses were conducted for the three main outcome domains, for all study designs and then after excluding observational studies and non-randomised trials. Prior to performing the MTC checks were undertaken as to whether or not the included studies formed a closed network using level 2 treatment categorisations with insufficient data to use individual (level 3) treatments as nodes. This meant that level 2 categorisations were used in the economic model. A full report of the MTC methods are reported elsewhere [11].

Table 1: Treatment categorisation used in the MTC analysis.

Studies evaluating mixed treatments (or combination therapy) were excluded, because of the uncertainty regarding the extent of interaction between the combined interventions. The analyses were performed by the Multi-parameter Evidence Synthesis Research Group in the Bayesian framework [15] and the modelling computed with Markov chain Monte Carlo stimulation methods using Winbugs [16].

The search for economic evaluations was conducted in parallel to the clinical effectiveness review. Given the nature and lack of homogeneity between included economic evaluations, a narrative review was performed on the included studies, with overall conclusions drawn. Detailed search methods including search protocols, search strategies and results of study selection are available as part of the full report of the systematic review [11].

The limitations of findings from the systematic review led to the development of a decision analytic model to estimate the relative cost-effectiveness of management strategies for patients with sciatica. The heterogeneous nature of the condition, the lack of recognised guidelines for the management of patients with sciatica and considerable variation within practice all made it extremely difficult to develop a model that accurately reflected current practice. The base-case analysis incorporated best available assumptions and data derived from the results of the systematic review, with sensitivity analysis undertaken to evaluate the sensitivity of the results to changes in important assumptions and input parameter values. The considerable level of uncertainty (seen with the wide variation in confidence intervals around the point estimates of global effect, as reported in the systematic review of clinical effectiveness [11]) restricted the development of a probabilistic model which could fully assess and quantify uncertainty.

The decision tree, highlighted in Figure 1, was used to model patient progression through sequential treatment pathways with the outcome of treatment (success/failure) determining the next treatment event and associated health state. The cost of managing patients within each state was reflected in the model, although it was not envisaged that patient progression will be seamless, or indeed linear and uni-directional in clinical practice.

The number of successful treatments was estimated over a 12-month period, together with the expected costs from the perspective of the UK National Health System (NHS) to determine interventions that would maximise health outcomes within the resource of the NHS. Out-of-pocket expenditures of over the counter medications (OTC), for example, were not included. This has important ramifications as it is assumed within the base-case model that ultimate treatment failures will resort to other therapies outside the conventional healthcare system, at no additional cost to the NHS. The influence of this assumption on modelled results was tested in sensitivity analysis.

A panel of 4 service providers known to the advisory group members were contacted by telephone to determine their usual approach to treatment in clinical practice. This information was used to inform which sequence of treatments to include in the economic model. Recruitment and access for the telephone survey was undertaken between June 2009 and September 2009. Three local health boards in Wales and six primary care trusts and hospital trusts in England were contacted. As required under the Research Governance Frameworks for England and Wales, permission was sought from each relevant research and development department prior to seeking and recruiting a range of service providers (e.g. spinal surgeons, physiotherapists, service commissioners).

The systematic review of clinical evidence [11] were used to generate a list of potential treatments For sciatica and guidance was consulted (e.g. MAP of Medicine). During the telephone interviews, clinicians were asked initially what treatments (including combination and sequence of treatments) they usually use, and, afterwards, if prominent treatments identified from previous reviews were not mentioned, they were asked if they have ever considered using these.

Treatment pathways

A series of 100+ independent scenarios were initially considered in relation to inactive control; comprising any combination of initial treatment followed by intermediate treatment which may be followed by epidural injection and then possibly disc surgery; or immediately referred for disc surgery following initial treatment. This paper focuses on a subset of three treatment pathways – initial treatments; initial treatments followed by intermediate treatments and invasive treatments (epidural and disc surgery); and initial treatments followed by disc surgery. The first pathway would involve management within primary care and revolve around what was termed “usual care”, with the use of analgesics and other medications considered , if appropriate, to attempt to secure symptom resolution. The treatments included within this pathway (see table 1 for further definition) were:

- Usual care education/advice
- Activity restriction
- Non-opioids
- Opioids

The second pathway would involve a stepped approach and include the use of intermediate treatments (offered in addition to the initial treatments provided within primary care) – and provided in secondary care out-patients by multi-disciplinary teams. The treatments included were:

- Manipulation
- Traction
- Passive physical therapy
- Active physical therapy
- Alternative treatments
- Biological agents

followed by more invasive treatment - epidural injections followed by disc surgery if there was no symptom resolution.

The third pathway would involve immediate referral for surgery following initial treatment in primary care to alleviate symptoms.

We could not identify any data to determine the proportion of patients managed through each pathway and therefore the treatment pathways represent the decision choices available for General Practionners (GPs) and their patients on presentation. Each of the pathways and the treatment variations available within them were compared with 'inactive control' (i.e. where a patient does nothing and takes into account the probability that symptoms resolve on their own accord) which, according to the findings from the MTC analysis, had a non-zero probability of symptom resolution. Indeed, counter intuitively this strategy was estimated to be more effective than usual care. In the base-case this reference strategy was assumed to incur no additional cost to the NHS.

Figure 1: Decision tree

Table 1: Treatment available within pathways

The focus for the economic evaluation was on the primary outcome of global effect used in the MTC analysis to define probabilities of success (overall improvement or resolution) of each treatment. The probabilities of success for each treatment were derived from the Winbugs output from the MTC which are fully reported elsewhere [11]. The Winbugs output provides a summary output of the posterior distributions of the relevant parameters. The probability of success is the median value of the posterior distribution of the global effect measure. The probabilities of success are shown in Table 2.

Table 2: Probabilities of success derived from the MTC analysis

Results were expressed as incremental cost per patient with symptoms successfully resolved. Analysis also included utility gain associated with symptom resolution, with results expressed as incremental cost per utility gained over a 12 month period. The heterogeneity in duration of follow up between studies and lack of evidence regarding relapse and recurrence rates made it difficult to extend the analysis beyond this time period, with the assumption made that the utility gained following successful treatment would continue for this period. This time period was also chosen to reflect the focus of the evaluation on different treatments within the period whereby treatments would be most effective for sciatica.

Costs

The costs associated with managing patients with sciatica were based on clinical opinion from clinical members of the research team and derived from published UK cost sources (2008-09 prices) [117,18,19] as shown in Table 3.

Table 3: Derivation of costs

Drug treatments were costed according to BNF list prices [17] at the time and calculated based on the dosage and durations in line with documented indications for use. Where required, it was assumed that dosage was based on an adult male of 65 kg. It was also assumed that paracetamol and ibuprofen were OTC medication; NSAIDs and Opioids would be prescribed as slow release tablets. Where multiple products were available, the least expensive option was applied in the base-case.

It was assumed that each prescription required a GP consultation and analgesics would be prescribed in accordance with the World Health Organisation (WHO) analgesic ladder; and consultations would be separate. For non-opioid analgesia (NSAIDs, muscle relaxants anti-depressants and anti-epileptic medication), two GP consultations were assumed with three consultations for opioid analgesia. Unit costs of GP consultations were taken from Curtis [18]. The

base-case analysis assumed that analgesics were prescribed separately. NSAIDs and opioids were costed based on single treatment for base-case analysis and multiple analgesics in the sensitivity analysis.

Intermediate care interventions reflected treatments provided in secondary care out-patient settings and included non-traditional and alternative therapies. Unit costs were taken from published NHS Reference Costs [19]. It was assumed that an initial consultant assessment would be undertaken with one follow up, with routine pathology and haematology blood tests and MRI (one area post contrast) performed for diagnosis. Passive and physical activity therapies, manipulation and traction were assumed to be physiotherapy-led interventions. Biological therapies are unlicensed for use in sciatica in the NHS. Therefore, a similar dosage and duration in line with documented indications for other spinal conditions, such as ankylosing spondylitis, was assumed. For the base-case analysis, it was assumed that a 12 week course of Adalimumab would be prescribed with sub-cutaneous injection by a practice nurse. For the sensitivity analysis, it was assumed to be an IV administration of Infliximab in an out-patient setting with prophylactic anti-histamine.

Intra-operative interventions which were included in the review of effectiveness and MTC analyses are extra interventions during disc surgery (e.g. introduction of steroid around exposed nerve root, exposed nerve root covered with a gel or membrane to reduce fibrosis) and are not routinely carried out in the UK NHS and were therefore excluded. Spinal cord stimulation involves implantation of an electrode and is only used if disc surgery has failed and therefore was also excluded from the model.

Epidural steroids were assumed to be a consultant out-patient intervention with one treatment being used in the base-case and three treatments in the sensitivity analysis. Surgical unit costs were taken from NHS Reference Costs [19]. It was assumed that an initial consultant assessment would be undertaken with one follow up, with routine pathology and haematology blood tests and MRI (one area post contrast) performed for diagnosis. A follow up consultant appointment was assumed with one GP follow up and practice nurse intervention for removal of sutures. Surgery was costed on in-patient extradural spinal minor with an average length of stay of 1.9 days for base-case and in-patient extradural spinal minor with an average length of stay of 3.33 days, for sensitivity analysis. The resultant costs are shown in table 4.

In the base-case, ultimate failures were assumed to have no additional cost to NHS, due to patient reliance on OTC treatments following failure; however the extent to which this is reflected in practice is subject to some debate. A sensitivity analysis related to this assumption utilised the NHS reference cost (mean £173; £109-205) of a consultant led face-to-face attendance for pain as an alternative model input, reflecting a referral of ultimate failures to a pain clinic.

Table 4: Cost summary

The utility values used in the model for symptoms and symptom resolution were derived from the literature review. However, the lack of specific utility values for sciatica symptoms pre-intervention and following symptom resolution was problematic. The baseline values were derived from those in van Hout et al. [20], using the EQ-5D, where the utility value at point of randomisation was 0.37 (taken as utility derived from treatment failure) and the best value obtained was 0.83 (as a result of treatment success). These values were adjusted within the sensitivity analysis to compensate for the lack of consensus within the literature [11]. The subsequent effects of non-responders at each stage of the pathway (estimated at 5-10%) were evaluated in the sensitivity analysis.

It was assumed in the base-case model that there was no reduction in utility for previous unsuccessful interventions, so a successful outcome was deemed to have utility 0.83 in baseline, regardless of how many interventions were required to achieve success. This was tested in sensitivity analysis.

A conventional approach to examining the cost-effectiveness of the treatment regimes was employed. Firstly, it was determined whether any of the regimes were dominated by others, having both lower costs and greater probability of success and secondly, whether any of the treatments were subject to extended dominance, where a more expensive treatment regime strategy had a lower incremental cost-effectiveness ratio than the less expensive regime. This process generated the 'efficiency frontier' of increasingly more costly and more effective regimes for the management of patients with sciatica.

Sensitivity analysis

A series of one-way sensitivity analyses were used to address uncertainty in the modelling assumptions and inputs. The baseline estimates utilised the best-case scenarios identified for cost

and then adjusted to reflect what was regarded as worst-case scenarios. Similarly, the probabilities of success were those determined from the WinBUGS output from the MTC in the baseline model and then adjusted to assess the impact on baseline findings. The utility values for symptoms and symptom remission were also adjusted to determine impact on baseline findings. Additional sensitivity analyses adjusted for the potential of reductions in effectiveness of intermediate therapies and/or surgery in the stepped approach (relative reduction: 10%) and utility achieved with symptom resolution only as a result of successive failures (relative reduction 25%).

Results

Whilst five full economic evaluations were identified in the systematic review [20,21,22,23, 24], the majority of evaluations were undertaken in conjunction with clinical trials with a lack of published decisions models. A full narrative review of the economic evidence has been published elsewhere [11]. There was considerable variation between each of the studies identified with relation to the management of patients with sciatica thus limiting the lessons that can be drawn from current evidence in order to understand the relative cost-effectiveness of current management strategies that reflect current practice.

With regard to the provider survey, the response rate was poor from England, with only three contacts established. Preliminary informal interviews were conducted with four service providers. However, these generated wide disparities in services (e.g. whether or not an intermediate care service was provided) and interventions offered (e.g. biologicals were not licensed for use and so would not be considered), resulting in difficulty in using individual service providers to contextualise a generic 'sequence of treatments' in relation to the findings emerging from the systematic review for the purposes of developing the structure for the economic model base case.

On review of these difficulties, the economic team felt that the provider survey would be better placed once the MTC analysis was completed in order to 'validate' the interventions/care approaches drawn from the review findings. However, owing to time constraints, these initial interviews were used along with input from the steering group (clinicians on the review team) to build up a staged treatment approach through the assumption of patient progression through primary, intermediate and specialist care.

The clinical review showed that no therapies can deliver 100% success; the model developed here demonstrated that similarly none of the treatment regimens tested can provide 100% success. In terms of initial treatments to alleviate symptoms and wait for symptom resolution, the most successful regime in the first treatment pathway was non-opioids, with a probability of success of 0.613, with 39 patients being unsuccessful for every 100 treated. When the second treatment pathway was considered, the most successful strategy was non-opioids, followed by biological agents followed by epidural/nerve block and disc surgery, with a probability of success of 0.996, that is 3 people out of every 1000 treated being unsuccessful.

Table 5 highlights the mean cost, probability of success and 12-month utility gain for all possible treatment strategies.

Table 5: Mean cost, probability of success and utility gain

The majority of treatment strategies were excluded on the grounds of strict dominance - where the next regime was both more effective and less costly - and by extended dominance - whereby a regime has an ICER that is higher than the next more effective regime. The regimes that represent the efficiency frontier are those based on non-opioids and are highlighted in Table 6:

Table 6: Cost effectiveness acceptability efficiency frontier

In terms of net benefit, four of the five strategies would be regarded as cost-effective if the ceiling ratio for an additional unit of utility gain over a 12-month period was <£5,100, and if the ceiling ratio for each additional success was <£2,500.

Sensitivity Analysis

The use of the highest cost estimates results in a similar overall picture and while the reported cost per quality adjusted year (QALY) estimates are higher, the stepped approaches based on non-opioids remain the most cost-effective strategies, as shown in Table 7.

Table 7: Switching treatments using highest cost scenarios

When the highest cost scenarios are employed, four of the five strategies are cost effective if the ceiling ratio for an additional success is <£6,000 and <£13,100 for an additional unit of utility gain.

While changes to the assumptions regarding zero additional cost to the NHS following ultimate failure, diminishing efficacy of intermediate therapies and surgery as a result of use following failure of prior treatments and decreased utility gains achieved for resolution of symptoms following failure of prior treatments resulted in changes to the absolute results (incremental costs, benefits and ICERs), which regimens were identified as most cost-effective did not change. The overall conclusions of cost-effectiveness were thus unaffected by these sensitivity analyses.

In order for the third pathway – immediate referral for surgery – to feature on the efficiency frontier, the costs associated with the treatment regimen following initial treatment with non-opioids would have to fall by 49% or the likelihood of success would have to increase by 10 percentage points to 0.95.

Adjusting utility values and probability of success had limited effect on baseline findings and would need to be increased outside the bounds of probability to affect basic premise that stepped approaches are more cost-effective than direct referral for surgery following initial treatments – as the differential in effectiveness for disc surgery is not sufficient to offset the differential in cost from conducting the procedure.

Discussion

The economic model has demonstrated that stepped approaches based on initial treatment with non-opioids represent the most cost-effective regimens for the treatment of sciatica. The treatment regimes that comprised the efficiency frontier were inactive control; non-opioids followed by alternative/non-traditional treatments; non-opioids followed by alternative/non-traditional treatments followed by epidural; non-opioids followed by alternative/non-traditional treatments followed by epidural followed by disc surgery; and, non-opioids followed by biological therapies followed by epidural and followed by disc surgery, although this latter regime would not be regarded as cost-effective when measured in terms of current cost-effectiveness thresholds. Further, the extent of potential net benefit from these treatment strategies would have relatively minor impact

on NHS budgets, and when a broader societal perspective is employed the extent of such net benefits is likely to be considerably more.

The extent to which changes in parameter estimates affect baseline findings are minor, with improbable reductions in cost and improvements in success rates required to suggest that direct referral to disc surgery represents a cost-effective approach to managing patients with sciatica.

However, there are a number of limitations associated with the analysis which raise important points for future health economic evaluations. Firstly, the nature of the evidence has meant that the modelled time perspective is limited to a 12-month horizon, with no evidence available to inform the inclusion of relapse and recurrence within the model. The perspective of the NHS does not enable the consideration of issues relating to work and productivity and the preferences of patients for symptom resolution and treatment duration. We also acknowledge the lack of exploration from a personal social services perspective and that possible additional costs associated with disc surgery were not included. Further work is needed to establish patient preferences relating to time taken to achieve success and the implications of failure after a series of treatments.

Secondly, the base-case assumption regarding ultimate failure having an additional zero cost to the NHS is contentious, but again lack of data and consensus has limited the evaluation of alternatives. It is highly likely that patients will resort to alternative therapies outside the conventional health care system. The base-case assumption that there was no reduction in utility for previous unsuccessful treatments is also subject to debate: assumptions had to be made on the limited information available; further work is needed to ensure the collection of health utility data as part of future trials and studies. Acknowledgement is made that the model makes the base-case assumption that when individual therapies are combined in sequence; effectiveness will be as high as stand-alone treatments. The lack of clinical evidence precluded a full examination of the effects of successive treatment failures and further work is required to assess the impact of treatment sequences.

Thirdly, one of the main strengths of the network meta-analysis is the wide range of treatment strategies used to treat sciatica that were not only considered in the same review but compared simultaneously in the same analysis. However, this was also its limitation. As the small number of relevant studies for some comparisons, statistical heterogeneity (within pair-wise comparisons) and potential inconsistency (between pair-wise comparisons) with the network means that the encouraging results for interventions such as biological agents should be interpreted with caution.

The findings for treatment such as surgery and epidural where more primary studies were available is more robust. Comparing all interventions in an economic analysis that is not based on a network meta-analysis means that less informal indirect analyses are made. Alternatively, the economic model and meta-analysis are often not conducted due to too much heterogeneity and decision making is based on reviewing the evidence in a disjointed fashion. In light of the limited evidence, pragmatic and basic assumptions were made in order to conduct the economic evaluation. We were interested in the average treatment effect of each 'treatment approach' and pooled different types of individual treatments (e.g. medication dosage) within each treatment approach. We therefore pooled clinically heterogeneous studies issuing a random-effects model, based on the assumption that different studies assessed different, yet related, treatment effects. However, included studies also varied in study design and risk of bias (methodological diversity). It was not possible to ascertain how much was due to clinical or methodological diversity and this needs to be taken into account in future work.

The inclusion of anti-inflammatory biological agents within our economic model could be seen as contentious. The systematic review of effectiveness considered any treatment used for sciatica in order to assess which is the most effective, irrespective of what is used in clinical practice in the UK. The economic evaluation reflected the aim of the systematic review to include all potentially effective treatments in the management of sciatica. The results of the systematic review demonstrated that although biological agents had high probability of being best and the largest effect estimated when compared to inactive control, these findings were associated with wide credible intervals, reflecting the lack of information on the estimation of effect size [25]. Sensitivity analysis indicated that removal of biological agents from the stepped approach made little difference to the cost-effectiveness results; these findings should be treated with caution.

Finally, it is acknowledged that the nature of the specified model is simplistic and fails to fully account for structural and parameter uncertainty and distributions. Further work is required to consider the implications of different modelling approaches in determining the relative cost-effectiveness of treatment regimens relating to managing patients with sciatica; particularly to assess longer-term and life-time horizons of the relative cost-effectiveness of different treatments for sciatica and transitions between health states during the course of sciatica. However, the extent to which the findings from this study are likely to change would require a dramatic change in the evidence base surrounding the range of treatments available for use within patients. The choice of

the global effects as the indicator of success can also be viewed as a limitation, although it again would probably not have changed the nature of the findings significantly.

The stepped approaches to managing sciatica based on an initial treatment with non-opioids represent the most cost-effective regimens relative to direct referral to disc surgery, with positive net benefits emerging if the acceptable ceiling ratio for an additional unit of success was <£2,500 with base-case costs and <£6,000 if higher costs were applied to the model. The strategy of referring patients who fail initial treatments directly to disc surgery is unlikely to be cost-effective, with highly improbable reductions in cost and/or rates of success being required to elevate these regimens to the efficiency frontier. However, these findings remain tentative and more research is required to develop the evidence base to inform more structurally appropriate economic models to inform decision making and to determine patient preferences regarding treatment durations and extent of invasive treatments that would be acceptable.

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Conflicts of Interest

None declared

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Table 1 Treatments considered within pathways

Pathways	Treatments (as defined by the level 2 categorisation of treatments performed in the MTC meta -analysis) [11]
Initial treatments	
	Inactive control
	Usual care
	Education/Advice
	Activity restriction
	Alternative/non-traditional (Acupunture)
	Non-opioids
	Opioids
Intermediate treatments	
	Manipulation
	Traction
	Passive Physical Therapy
	Active Physical Therapy
	Biological agents
Invasive therapies	
	Epidural/nerve Block
	Disc surgery

Table 2: Probabilities of success derived from the MTC analysis

Pathways	Treatments	Probability of success	Probability of failure
	Inactive control	0.3828	0.6172
Initial treatments			
	Usual care	0.3393	0.6607
	Education/Advice	0.5025	0.4975
	Activity restriction	0.4411	0.5589
	Non-opioids	0.6129	0.3871
	Opioids	0.4985	0.5015
Intermediate treatments			
	Alternative/non-traditional treatments	0.8523	0.1477
	Biological agents	0.9074	0.0926
	Manipulation	0.7518	0.2482
	Traction	0.4277	0.5723
	Passive Physical Therapy	0.4147	0.5853
	Active Physical Therapy	0.4043	0.5957
Invasive therapies			
	Epidural	0.6577	0.3423
	Disc surgery	0.633	0.367

Table 4: Cost summary

Treatments	Base case (£)	Sensitivity analysis (£)
Initial treatments		
Inactive control	0	0
Usual care	73.74	80.68
Education/Advice	81	81
Activity restriction	70	70
Alternative/non-traditional	70	70
Non-opioids	122.23	129.33
Opioids	130.26	152.71
Biological agents	1646.74	3467.24
Intermediate treatments		
Manipulation	349	578
Traction	349	578
Passive Physical Therapy	349	578
Active Physical Therapy	349	578
Surgery		
Epidural	602.76	990.28
Disc surgery	1433.66	3794.71

Table 3: Derivation of costs

Primary Care					
Description		*Unit Cost (£)*	*Cost (£)*		*Source of data*
GP consultation for all patients (within 6 weeks)		£35	Average 2 consultations (varies between 1 and 3) =£70		Curtis [18]
GP consultation for patients referred to intermediate care/surgery (+/- 6 weeks)		£35	Referral usually triggered after 3 consultation = £105		Curtis [18]
GP contact following discharge from intermediate care/ surgery		£35	Typically one follow-up to GP for post-op analgesia/Sick note		Curtis [18]
Other primary HP contact (surgery patients only)		£10	Typically one intervention to remove suture by practice nurse		Curtis [18]
Prescriptions					
Drugs	*Description*	*Dose*	*Cost (£)*	*Continuing therapy*	*Source of data*
Paracetamol and/or Ibuprofen	Likely to be OTC and patient self management for all patients but GP would start as initial/ continuing therapy in first 6 weeks	Paracetamol: Dosage 4g per 24 hours @ 6 week prescription = approx 336 tablets Ibuprofen: dosage 1600mg per 24 hours@6 week prescription= approx=168 tables (if 400mg tabs)	£3.57 (based on 16 tabs =£0.17) £3.74 (based on 84 400mg tabs =£1.87)	1 week cost £0.60 1 week cost £0.62	BNF 59 [19]
Mild opioids (codeine phosphate)	Prescribed if initial analgesia is not working	240mg per 24 hours@6 weeks=168tabs (if 60mg tablets) If added in at second visit - 4 weeks prescription[2]	6 week prescription= £11.88(28 60 mg tabs =£1.98) 4 weeks £7.92	£1.98	BNF 59 [19]
Other NSAIDs (Naproxen)	Prescribed if initial analgesia is not working and/or with mild opioid	1250mg per 24 hours @ 6 weeks = 210 tablets 4 weeks= 140 tabs	6 weeks = £10.65(based on 250mg 28 tab) 4 weeks=£7.10	£1.775	BNF 59 [19]
Strong opioids (morphine) - considered only after no success with mild opioids/combinations with NSAIDs	Often in combination with co-analgesic		£9.61 (MST 30mg day) for 2 weeks	£4.805	BNF 59 [19]

	Amitriptyline *Or gabapentin*		£1.04 (25mg per day) for 2 weeks) £7.88 for two weeks (based on titrating dose from 900mg towards maximum dose)	£0.52 £5.52 (based on maximum dose of 3.6g as maintenance)	
Diazepam	For muscle spasm	6mg per 24 hours but prn		£1.96	BNF 59 [19]
Intermediate care					
Intervention	*Description*		*Cost (£)*		*Source of data*
Initial consultation	First attendance consultant led (110N)		£124 (94-147) - skill mix can vary		NHS 2008-9 [20]
	First physiotherapy contact (650A)		£55 (53-53)		NHS 2008-9 [20]
MRI	RA027- one area post contrast		£195 (£142-239)		NHS 2008-9 [20]
Pathology	Haematology biochemistry		£3 (£2-4) £1 (1-2)		NHS 2008-9 [20]
Follow up	Consultant led (110N)		£86 (64-99)		NHS 2008-9 [20]
	Follow up physiotherapy		£19 (19-19)		NHS 2008-9 [20]
Biological therapies	Unlicensed for use in patients with sciatica in the NHS. Therefore, assumed similar dosage and duration in line with documented indications for other spinal conditions such as ankylosing spondylitis. For Adalimumab, it was assumed to be a 12 week course with sub-cutaneous injection by a practice nurse. For Infliximab (worst case), it was assumed to be an IV administration in an out-patient setting with prophylactic anti-histamine.		£1647 £2219		BNF 59 [19] NHS 2008-9 [20]
Epidural steroids	Out-patient Intermediate pain procedure (ABO5Z)		£190 (125-205) - up to 3		NHS 2008-9 [20]

Surgery			
Procedure		*Cost (£)*	*Source of data*
Day case extradural spinal minor (1) without CC- HCO6c		£980 (570-954)	NHS 2008-9 [20]
In-patient extradural spinal minor (1) without CC (HCO6c) Average 1.9 days stay		£1,657 (1,956-2,314)	NHS 2008-9 [20]
In patient extradural spinal minor (2) without CC (HCO6c) Average 3.33 days stay		£2,858 (1,699-3,184)	NHS 2008-9 [20]
Follow-up consultant led appointment		£86 (64-99)	NHS 2008-9 [20]

Table 5: Mean cost, probability of success and utility gain (1000 patients)

Treatments	Mean cost	No. of successes
Inactive control	0	
Usual care	73740	
Usual care and active physical therapy	304324	
Usual care and passive physical therapy	304324	
Usual care and traction	304324	
Usual care and manipulation	304324	
Usual care and alternative/non-traditional treatments	304324	
Usual care and biological agents	1161741	
Usual care and active physical therapy and epidural	541558	
Usual care and passive physical therapy and epidural	537416	
Usual care and traction and epidural	532239	
Usual care and manipulation and epidural	403168	
Usual care and alternative/non-traditional treatments and epidural	363145	
Usual care and biological agents and epidural	1198618	
Usual care and active physical therapy and epidural and disc surgery	738621	
Usual care and passive physical therapy and epidural and disc surgery	731039	
Usual care and traction and epidural and surgery	721562	
Usual care and manipulation and epidural and surgery	485275	
Usual care and alternative/non-traditional treatments and epidural and surgery	412005	
Usual care and biological agents and epidural and surgery	1229251	
Usual care and disc surgery	1040172	
Activity restriction	70000	
Activity restriction and active physical therapy	265056	
Activity restriction and passive physical therapy	265056	
Activity restriction and traction	265056	
Activity restriction and manipulation	265056	
Activity restriction and alternative/non-traditional treatments	265056	
Activity restriction and biological agents	990363	
Activity restriction and active physical therapy and epidural	465737	
Activity restriction and passive physical therapy and epidural	462233	
Activity restriction and traction and epidural	457854	
Activity restriction and manipulation and epidural	348670	
Activity restriction and alternative/non-traditional treatments and epidural	314814	
Activity restriction and biological agents and epidural	1021558	
Activity restriction and active physical therapy and epidural and disc surgery	632437	
Activity restriction and passive physical therapy and epidural and disc surgery	626023	
Activity restriction and traction and epidural and surgery	618006	
Activity restriction and manipulation and epidural and surgery	418126	
Activity restriction and alternative/non-traditional treatments and epidural and surgery	356146	
Activity restriction and biological agents and epidural and surgery	1047471	
Activity restriction and disc surgery	887525	

Opioids	130260
Opioids and active physical therapy	305284
Opioids and passive physical therapy	305284
Opioids and traction	305284
Opioids and manipulation	305284
Opioids and alternative/non-traditional treatments	305284
Opioids and biological agents	956100
Opioids and active physical therapy and epidural	485354
Opioids and passive physical therapy and epidural	482210
Opioids and traction and epidural	478281
Opioids and manipulation and epidural	380310
Opioids and alternative/non-traditional treatments and epidural	349931
Opioids and biological agents and epidural	984092
Opioids and active physical therapy and epidural and disc surgery	634934
Opioids and passive physical therapy and epidural and disc surgery	629179
Opioids and traction and epidural and surgery	621985
Opioids and manipulation and epidural and surgery	442633
Opioids and alternative/non-traditional treatments and epidural and surgery	387018
Opioids and biological agents and epidural and surgery	1007343
Opioids and disc surgery	863824
Education and advice	81000
Education and advice and active physical therapy	254628
Education and advice and passive physical therapy	254628
Education and advice and traction	254628
Education and advice and manipulation	254628
Education and advice and alternative/non-traditional treatments	254628
Education and advice and biological agents	900253
Education and advice and active physical therapy and epidural	433262
Education and advice and passive physical therapy and epidural	430143
Education and advice and traction and epidural	426245
Education and advice and manipulation and epidural	329056
Education and advice and alternative/non-traditional treatments and epidural	298919
Education and advice and biological agents and epidural	928021
Education and advice and active physical therapy and epidural and disc surgery	581649
Education and advice and passive physical therapy and epidural and disc surgery	575939
Education and advice and traction and epidural and surgery	568803
Education and advice and manipulation and epidural and surgery	390882
Education and advice and alternative/non-traditional treatments and epidural and surgery	335710
Education and advice and biological agents and epidural and surgery	951088
Education and advice and disc surgery	808713
Non-opioids	122230
Non-opioids and active physical therapy	257328

Non-opioids and passive physical therapy	257328
Non-opioids and traction	257328
Non-opioids and manipulation	257328
Non-opioids and alternative/non-traditional treatments	257328
Non-opioids and biological agents	759683
Non-opioids and active physical therapy and epidural	396322
Non-opioids and passive physical therapy and epidural	393895
Non-opioids and traction and epidural	390862
Non-opioids and manipulation and epidural	315240
Non-opioids and alternative/non-traditional treatments and epidural	291791
Non-opioids and biological agents and epidural	781289
Non-opioids and active physical therapy and epidural and disc surgery	594629
Non-opioids and passive physical therapy and epidural and disc surgery	588740
Non-opioids and traction and epidural and surgery	581379
Non-opioids and manipulation and epidural and surgery	397865
Non-opioids and alternative/non-traditional treatments and epidural and surgery	340960
Non-opioids and biological agents and epidural and surgery	812116
Non-opioids and disc surgery	688457

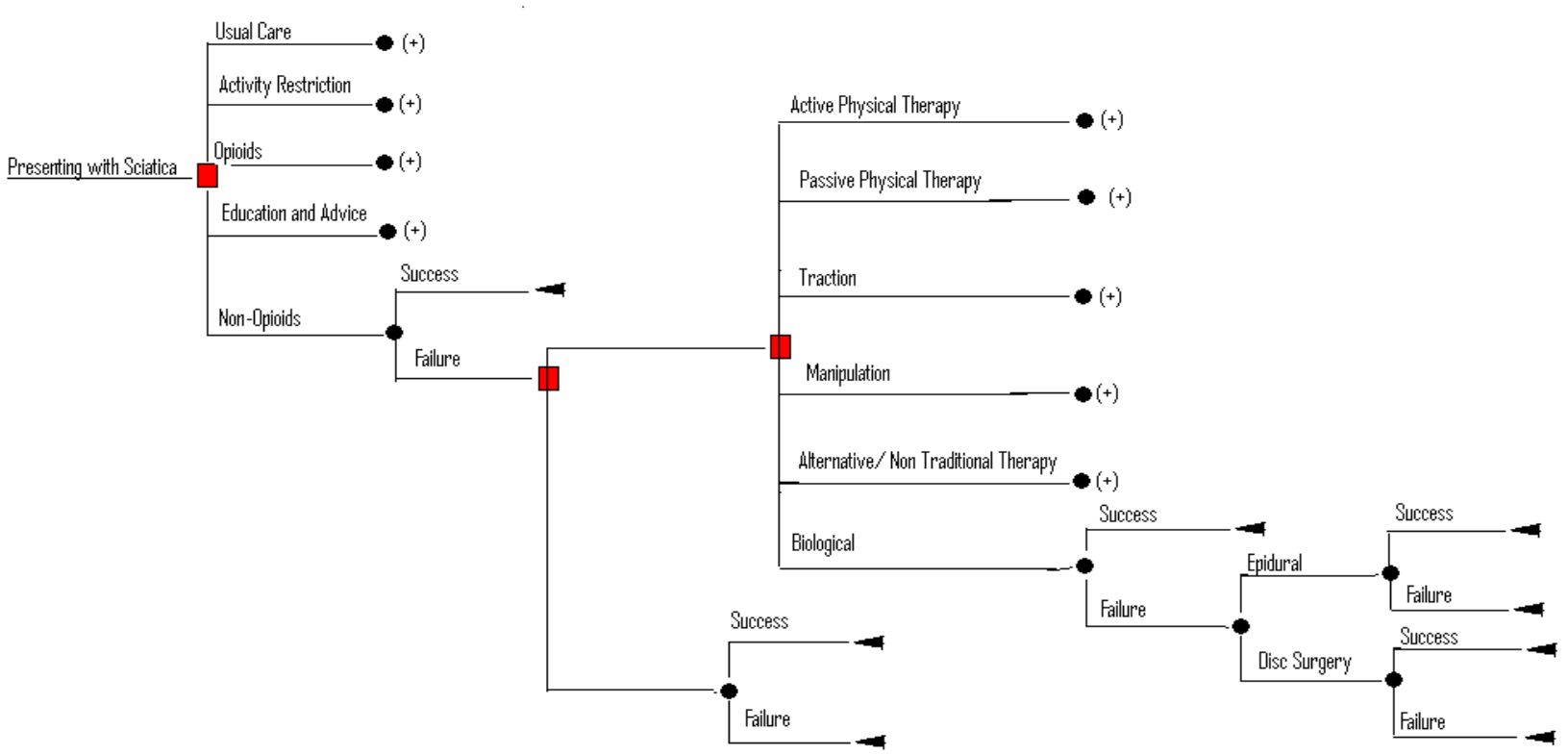
Table 6 Cost effectiveness acceptability efficiency frontier

Treatment	**Cost**	Prob.**success**	Utility gain	**Inc cost**	**inc success**	**ICER**	**inc utility gain**	**ICER**
Inactive control	0	383	176					
Non-opioids and alternative/non-traditional treatments	257328	943	434	257328	560	459	258	999
Non-opioids, alternative/non-traditional treatments and epidural	291791	980	451	34463	38	916	17	1992
Non-opioids, alternative/non-traditional treatments, epidural and disc surgery	320418	993	457	28627	12	2311	6	5023
Non-opioids, biological therapies, epidural and disc surgery	799237	995	458	478819	3	178700	1.23	388478

Table 7 Cost-effectiveness efficiency frontier using highest cost scenarios

Treatment	**Cost**	**utility gain**	**success**	**Inc cost**	**Inc success**	**ICER**	**inc utility**	**ICER**
Inactive control	0	176	383					
Non-opioids	129330	282	613	129330	230	562	106	1222
Non-opioids and alternative/non-traditional treatments	353074	434	943	223744	330	678	152	1474
Non-opioids and alternative/non-traditional treatments and epidural	409693	451	980	56619	38	1506	17	3273
Non-opioids and alternative/non-traditional treatments and epidural and surgery	483959	457	993	74266	12	5995	6	13032
Non-opioids and biological agents and epidural and surgery	1553556	458	995	1069598	3	399184	1	867791

Figure 1: Decision-tree



Decision nodes (red square): represents an event with at least two possible alternatives which are under our control. They are usually where a choice is made by a patient/clinician/manager relating to how a patient is diagnosed/treated/not treated
Chance nodes (black circle): represents an event with at least two possible outcomes where the outcome is out of our control/about which there is uncertainty. For example, a test result can be positive/negative or a patient can respond or not respond to a treatment
Truncated branch: the (+) indicates that the previous branches are repeated. In this diagram same success/failure options after each type of treatment
End node (black triangle): this is a final point that terminates the branching – the end of the modelled pathway. This is where final costs or health outcomes/benefits are evaluated.