Health Technology Assessment 2005; Vol. 9: No. 33

Cost-effectiveness and safety of epidural steroids in the management of sciatica

C Price, N Arden, L Coglan and P Rogers

August 2005

Health Technology Assessment
NHS R&D HTA Programme

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Cost-effectiveness and safety of epidural steroids in the management of sciatica

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Declared competing interests of authors: none

Published August 2005

This report should be referenced as follows:

Price C, Arden N, Coglan L, Rogers P. Cost-effectiveness and safety of epidural steroids in the management of sciatica. *Health Technol Assess* 2005;**9**(33).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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ISSN 1366-5278

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Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

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Objectives: To investigate the clinical effectiveness of epidural steroid injections (ESIs) in the treatment of sciatica with an adequately powered study and to identify potential predictors of response to ESIs. Also to investigate the safety and cost-effectiveness of lumbar ESIs in patients with sciatica.

Design: A pragmatic, prospective, multicentre, double-blind, randomised, placebo-controlled trial with 12-month follow-up was performed. Patients were stratified according to acute (<4 months since onset) versus chronic (4–18 months) presentation. All analyses were performed on an intention-to-treat basis with last observation carried forward used to impute missing data.

Setting: Rheumatology, orthopaedic and pain clinics in four participating centres: three district hospitals and one teaching hospital in the south of England.

Participants: Total of 228 patients listed for ESI with clinically diagnosed unilateral sciatica, aged between 18 and 70 years, who had a duration of symptoms between 4 weeks and 18 months.

Interventions: Patients received up to three injections of epidural steroid and local anaesthetic (active), or an injection of normal saline into the interspinous ligament (placebo).

Main outcome measures: The primary outcome measure was the Oswestry Disability Questionnaire (ODQ); measures of pain relief and psychological and physical function were collected. Health economic data on return to work, analgesia use and other interventions were also measured. Quality-adjusted life-years (QALYs) were calculated using the SF-6D, calculated from the Short Form (SF-36). Costs per patient were derived from figures supplied by the centres' finance departments and a costings exercise performed as part of the study. A cost–utility analysis was performed using the SF-36 to calculate costs per QALY.

Results: ESI led to a transient benefit in ODQ and pain relief, compared with placebo at 3 weeks ($p = 0.017$, number needed to treat = 11.4). There was no benefit over placebo between weeks 6 and 52. Using incremental QALYs, this equates to an additional 2.2 days of full health. Acute sciatica seemed to respond no differently to chronic sciatica. There were no significant differences in any other indices, including objective tests of function, return to work or need for surgery at any time-points. There were no clinical predictors of response, although the trial lacked sufficient power to be confident of this. Adverse events were uncommon, with no difference between groups. Costs per QALY to providers under the trial protocol were £44,701. Costs to the purchaser per QALY were £354,171. If only one ESI was provided then costs per QALY fell to £25,745 to the provider and £167,145 to the purchaser. ESIs thus failed the QALY threshold recommended by the National Institute for Health and Clinical Excellence (NICE).

Conclusions: Although ESIs appear relatively safe, it was found that they confer only transient benefit in symptoms and self-reported function in a small group of patients with sciatica at substantial costs. ESIs do not provide good value for money if NICE recommendations are followed. Additional research is suggested into the epidemiology of radicular pain, producing a register of all ESIs, possible subgroups who may benefit from ESIs, the use of radiological imaging, optimal early interventions, analgesic agents and nerve root injections, the use of cognitive behavioural therapy in rehabilitation, improved methods of assessment, a comparative cost–utility analysis between various treatment strategies, and methods to reduce the effect of scarring and inflammation.

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List of abbreviations

A	active
ANOVA	analysis of variance
CBT	cognitive behavioural therapy
ESI	epidural steroid injection
HAD	Hospital Anxiety and Depression Scale
IASP	International Association for the Study of Pain
ITT	intention-to-treat
LOCF	last observation carried forward
MPQ	McGill Pain Questionnaire
MRI	magnetic resonance imaging
NHSIA	National Health Service Information Authority
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
ODQ	Oswestry Disability Questionnaire
PDPH	postdural puncture headache
Pl	placebo
QALY	quality-adjusted life-years
RCT	randomised controlled trial
SD	standard duration
SF-36	Short Form 36
SG	standard gamble
SLR	straight leg raise
VAS	visual analogue scale (for both back and radicular pain)

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Sciatica is a common cause of pain and disability. Epidural injections of corticosteroids (ESIs) commonly are used to treat sciatica. In 2002/03 there were 45,948 ESIs performed within the NHS. A systematic review and meta-analysis of previous trials found that there was weak benefit from ESIs, but most trials were underpowered. Safety and cost-effectiveness have not been evaluated.

Objectives

The objectives of this study were:

- to verify the clinical effectiveness of ESIs in the treatment of sciatica with an adequately powered study
- to identify potential predictors of response to ESIs
- to investigate the safety of lumbar ESIs in patients with sciatica
- to evaluate the cost-effectiveness of lumbar ESIs.

Methods

Design

A pragmatic, prospective, multicentre, double-blind, randomised, placebo-controlled trial with 12-month follow-up was performed. The study included 228 patients listed for ESI with clinically diagnosed unilateral sciatica, aged between 18 and 70 years, who had a duration of symptoms between 4 weeks and 18 months. Patients were stratified according to acute (<4 months since onset) versus chronic (4–18 months) presentation. All analyses were performed on an intention-to-treat basis with last observation carried forward used to impute missing data. Data were collected from dropouts, cross-overs and withdrawals at 52 weeks to give as much information as possible on long-term follow-up.

Setting

The study took place in rheumatology, orthopaedic and pain clinics in four participating centres: three district hospitals and one teaching hospital in the south of England.

Interventions

Patients received up to three injections of epidural steroid and local anaesthetic (active), or an injection of normal saline into the interspinous ligament (placebo).

Main outcome measures

The primary outcome measure was the Oswestry Disability Questionnaire (ODQ); measures of pain relief and psychological and physical function were collected. Health economic data on return to work, analgesia use and other interventions were also measured. Quality-adjusted life-years (QALYs) were calculated using the SF-6D, calculated from the Short Form (SF-36). Costs per patient were derived from figures supplied by Trust finance departments and a costings exercise performed as part of the study. A cost–utility analysis was performed using the SF-36 to calculate costs per QALY.

Results

ESI led to a transient benefit in ODQ and pain relief, compared with placebo at 3 weeks ($p = 0.017$, number needed to treat = 11.4). There was no benefit over placebo between weeks 6 and 52. Using incremental QALYs, this equates to an additional 2.2 days of full health. Acute sciatica seemed to respond no differently to chronic sciatica. There were no significant differences in any other indices, including objective tests of function, return to work or need for surgery at any time-points. There were no clinical predictors of response, although the trial lacked sufficient power to be confident of this. Adverse events were uncommon, with no difference between groups.

Costs per QALY to providers under the trial protocol were £44,701. Costs to the purchaser per QALY were £354,171. If only one ESI was provided then costs per QALY fell to £25,745 to the provider and £167,145 to the purchaser. ESIs thus fail the QALY threshold recommended by the National Institute for Health and Clinical Excellence (NICE).

Conclusions

Although ESIs are relatively safe, it was found that they confer only transient benefit in symptoms and self-reported function in a small group of patients with sciatica at substantial costs. ESIs do not provide good value for money to the NHS as determined by NICE guidelines.

Implications for healthcare

The results of this study suggest the following.

- There is little evidence to support the use of ESIs in acute sciatica; better patient education, reinforcement of analgesic strategies and the instruction to keep as active as possible are important.
- Owing to the short-term benefit from ESIs and lack of predictors of response, the routine use of ESIs in sciatica needs to be reviewed urgently and its place re-evaluated.
- Given the severity of impact on psychophysical functioning these patients require a multidisciplinary assessment and better analgesic and rehabilitation strategies.
- A national registry of all ESIs may be a suitable method for collecting appropriate safety data.
- The use of ESIs to defer surgery requires review.
- Repeat ESIs do not appear to be effective.
- The costs of ESIs to purchasers as used in their present form, do not, in the authors' opinion, represent good value for money and indeed fail the QALY threshold.

Recommendations for research

There are a number of areas that would benefit from additional research:

- Further work on the epidemiology of radicular pain is needed so that patients can be presented with better information on prognosis.
- A register of all ESIs should be developed so that the true incidence of major complications can be accurately determined.
- Subgroups who may benefit from ESIs may be identified through very large trials: these need not have long-term follow-up, but a wider range of assessment tools may be necessary to detect small changes in function. A subgroup analysis of acute and chronic patients may be one of these groups.
- Although previous studies have been inconclusive, the use of radiological imaging may improve accuracy and should be investigated further in larger studies with respect to outcome.
- Further work on the optimal early interventions may reduce the incidence of severe persistent sciatica. This is likely to require a multidisciplinary approach even at an early stage with involvement of vocational rehabilitation.
- A systematic review of analgesic agents and nerve root injections would determine the research agenda for these two potential analgesic strategies.
- The use of cognitive behavioural therapy in rehabilitation should be explored further.
- Exploration of improved methods of assessment to include investigation of cognitive content and processing in those with sciatica may better determine specific rehabilitative strategies.
- A comparative cost–utility analysis between various treatment strategies for sciatica would help purchasers in decision-making.
- Other more novel methods to reduce the effect of scarring and inflammation should be explored.

Chapter 1

Scientific background

Definition and epidemiology

Sciatica is a common cause of pain and disability. Sciatica is defined as unilateral, well-localised leg pain that approximates to the dermatomal distribution of the sciatic nerve and normally radiates to the foot or toes. It is often associated with numbness or paraesthesia in the same distribution.[1] In the majority of cases the natural history of the disease is of spontaneous resolution; however, some studies have reported that 30% had significant symptoms at 1 year, with 20% out of work and 5–15% requiring surgery.[2,3] Little work has been done on the epidemiology of sciatica in the UK; however a Finnish study reported the lifetime prevalence of sciatica to be 5.3% in men and 3.7% in women with sciatica, representing 6% of the total work disability of the population.[4] The cost of conservatively treated sciatica was estimated at £30,000 in a 1997 US study.[5]

Sciatica was initially thought to occur predominantly as a result of prolapsed lumbar vertebral disc causing compression of the nerve root, leading to neural ischaemia, oedema and eventually to chronic inflammation, scarring and perineural fibrosis. It is now evident that sciatica can occur in the absence of direct nerve root compression, possibly as a result of the release of phospholipase A_2 and other proinflammatory agents from a damaged disc leading to nerve root inflammation and oedema.[6,7] Pain occurs because of chronic, repetitive firing of the inflamed nerve root. Persistent neuropathic pain is likely as a result of this process, but this has not been well explored. There have been many studies considering risk factors for the development of low back pain. Some issues have been considered for sciatica. Mental stress has been shown to predict low back pain, but not disc prolapse.[8] There is no direct evidence of any relationship between sciatica and smoking. Many studies have shown a higher prevalence of early spine degeneration and disc prolapse with driving. This has been reviewed and it seems that exposure to vibration is the critical factor.[9]

Rationale for the use of epidural corticosteroids

The treatment of sciatica has centred around the above proposed pathophysiological mechanisms. In the presence of significant compression surgical decompression is traditionally carried out. In the presence of nerve root irritation the established procedure is treatment of radicular pain by analgesia and physical therapy, often proceeding to epidural steroid injection (ESI) if there is no improvement. None of these strategies has complete success, but ESIs have long been regarded as a useful addition to therapy. ESIs are one of the most common procedures performed in the UK, with 45,948 recorded in the NHS 2002/03.[10] Of these, 14,870 were specifically coded for sciatica. The epidural space is situated deep to the ligamentum flavum above the layers of meninges that envelop the spinal cord and its adjacent nerve roots as they emerge from the spinal cord. Drugs are deposited peridurally. The majority of epidural injections performed for sciatica use a local anaesthetic agent and a long-acting corticosteroid. It is thought that the majority of the therapeutic benefit achieved by epidural injections is due to the anti-inflammatory effects of corticosteroids in reducing perineural inflammation. However, local anaesthetic agents alone may have some effect by reducing painful muscle spasm, interrupting repetitive radicular firing and interfering with any sympathetic elements. Lee and colleagues found that in the rat model the mechanism of action of epidural steroid is inhibition of phospholipase A_2 activity.[11] It is not clear what proportion of benefit is due to the corticosteroid and to the local anaesthetic agent, but the combination of a corticosteroid and local anaesthetic agent was found to be more effective than local anaesthetic alone in one small study.[12]

Previous studies of epidural corticosteroids

Initial uncontrolled studies with epidural steroids gave promising results; however, the results of clinical trials have proved inconclusive. Many clinical trials have been performed, several of which have studied sciatica in isolation and have been randomised and blinded. Of these, four found significant improvement with epidural steroids and five found little long-term benefit.[13–21] There are several methodological differences between these published studies that make it difficult to draw any firm conclusion from them:

- Statistical power: the majority of the studies have had limited statistical power to detect anything less than major treatment effect sizes, with only two of the studies containing 50 or more patients in each arm.[18,19]
- Placebo: the placebo used in each study has varied from intraligamentous saline to epidural anaesthetic in equal volumes to the active arm, making comparisons between studies difficult.[14,15,17,19]
- Study population: the populations studied have varied between studies from radiologically proven disc lesions to sciatica diagnosed clinically with no imaging.[14–20,22] Individual studies have often recruited heterogeneous populations (including the chronicity of symptoms) but no attempt was made to identify any subgroups that may have responded.
- Route of injection: both the caudal and lumbar approaches have been used in previous studies.[14–21,23] There is some suggestion that the lumbar approach may be a more accurate approach to reach the epidural space and often places the steroid closer to the inflamed root.
- Follow-up: many studies have used only extremely short-term follow-up at 24–48 hours as their primary outcome measure; furthermore, the timing of the assessment of the primary outcome measure has varied markedly between studies.[18,19]
- Outcome measures have varied between studies.[13,14,18–20,22]

A meta-analysis reached the conclusion that epidural steroids offer short-term benefit.[23] However, it did not address several of the flaws mentioned above, and its validity is questionable owing to the heterogeneity of the studies incorporated in it.[24] A systematic review included many of the above criticisms, but failed to distinguish between low back pain and sciatica, which may have differing aetiologies.[25] In patients obtaining partial relief of symptoms, further benefit has been obtained by repeated epidurals, up to a total of three.[26,27]

There has been the suggestion that the insertion of local anaesthetic and steroid blindly into the epidural space using a translumbar approach is highly inaccurate.[28] However, lumbar epidurals are highly accurate as long as obese patients are excluded. When using the lumbar approach to the epidural space 93% of injections are correctly placed, increasing to 97% when the operator was confident of the placement. This is not the case for the caudal approach, when the figures are only 64% and 85%, respectively.[29]

Predictors of response

Predictors of a poor prognosis and response to treatment in sciatica have been extensively investigated. Vroomen and colleagues found that for those presenting in primary care a disease duration of more than 30 days, increased pain on sitting and more pain on coughing, sneezing or straining predicted poor outcome at 3 months. The straight leg raise (SLR) test and, to a lesser degree, the reversed SLR test, were the most consistent examination findings associated with poor outcome.[30]

Prediction of outcome of those patients presenting to secondary care facilities varies according to the intervention offered. In surgical treatment of those with sciatica, duration of leg pain greater than 8 months, sick leave greater than 6 months, nerve root compression, preoperative co-morbidity and female gender predict poor functional outcome.[31,32] However, no predictors of outcome were found in those offered rehabilitation.[33] No study has directly identified a subgroup of patients who respond better to corticosteroid, although it is postulated that those with perineural oedema rather than direct neural compression should respond well. There is evidence to support this hypothesis as three studies including patients with radiologically proven disc lesions have reported no benefit from epidural injection.[16,18,19] Jamison and Vade Boncoeur Ferrante looked at predictors of poor short-term outcome from ESI for low back pain and sciatica.[34] It appears that a large number of treatments, and pain worsened by activity and coughing, may be factors. Beliveau suggested that those with chronic disease (over 6 months) may do better.[17] Prediction of those who are at risk of long-term disability, which engenders the greatest costs, has been little researched in sciatica.

Thus, it appears that in terms of clinical effectiveness steroids may benefit those who have less severe disc prolapse, that the benefit may be short to medium term only, and that the effect may be relatively small. Chronicity of the symptoms may be a factor in determining response to injection.

The place of magnetic resonance imaging (MRI) in degenerative disc disease has not been fully established. MRI-demonstrated lesions correspond well with operative findings; however, the majority of disc bulges and protrusions are asymptomatic.[35] Although MRI findings correlate well with clinical findings for site and level of a disc herniation, they correlate poorly with the severity of symptoms.[34] This is thought to be due to the fact that pain is more due to inflammation than to compression. The role of MRI in predicting the long-term outcome of sciatica is not fully understood.[4,36]

Safety of ESIs

ESIs have been the subject of debate on the grounds of safety. Many reviews have been published concerning risks associated with epidural and intrathecal interventions. ESIs accounted for 40% of all chronic pain management claims in a closed claim analysis.[37] Although serious complications are rare, they must be considered.

First, there are risks related to the procedure itself. These include inadvertent needle trauma to related structures such as nerves and blood vessels. Haematomas, nerve damage and potential paraplegia are possibilities. Organ damage has also been reported. It has been suggested that diabetic patients receiving epidural steroids are predisposed to infection.[38] Therefore, a strict aseptic technique together with the exclusion of high-risk patients should be considered mandatory for the injection of epidural steroids. Postdural puncture headache (PDPH) presents a more frequent complication (0.4%).[39] This is often self-limiting, requires overnight admission to hospital and occasionally requires interventions such as an epidural blood patch. Very occasionally the symptoms do not resolve and surgical intervention could be required to repair a dural tear. Many of these patients have had previous surgery to their backs. Scarring and adhesions can seriously restrict the degree of spread of the epidural steroids. This could result in an increased rate of inadvertent dural puncture.

Second, there are risks to be considered that are specific for the drugs chosen for epidural injection. In reality, epidural steroids have probably received a disproportionate amount of public scrutiny over recent years. There is little evidence for concern in the concentrations currently used. There is debate over which steroid to inject into the epidural space. This is centred around the possibility that the preservative could have neurotoxic properties. The drugs used are depot preparations. They are suspended in polyethylene glycol and a preservative can be added called benzyl alcohol (multidose vials). Animal studies do not suggest that the clinically relevant concentrations are neurotoxic.[40] Based on this information the concentrations used in the UK are too low to give any cause for concern. Triamcinolone contains the least amount of preservative of the available steroids. Inadvertent intrathecal injections have been considered to potentially cause arachnoiditis. The incidence is very low for intrathecal steroids and probably irrelevant compared with the frequency of idiopathic arachnoiditis.[41] The extrusion of intervertebral disc contents has been implicated.[42] The glycoproteins induce antibody production and a reactive inflammation follows. This inflammatory process is also further enhanced by increases in phospholipase A_2. There is no evidence that epidural steroids cause arachnoiditis. A review of this issue concluded that the majority of complications with steroids occur as a result of intrathecal injection and not epidural injection.[43] Although intrathecal injection may occur with epidural injection it was considered unlikely. The complications that have been reported with ESIs are epidural abscess, meningitis, hypercorticism and allergy.[44] These are so rare that they are the subject of isolated case reports.

Economic evaluation of treatments for sciatica

With regard to cost-effectiveness little work has been done specifically looking at sciatica. One study examined the cost-effectiveness of ESIs. Lafuma and co-workers found that adding an epidural injection as a first line treatment to rest and a non-steroidal anti-inflammatory drug for the treatment of lumbosciatic syndrome requiring in-hospital management results in additional costs and no gain in efficacy.[45] This is not common practice. The previous studies of epidurals have been heterogeneous in design and outcome measures and have failed to address costs.

Chapter 2

General methods

Further details of the protocol for this investigation are given in Appendix 1.

The hypothesis was that epidural steroids are neither more cost-effective nor more clinically effective than placebo in the treatment of sciatica.

The objectives of the study were to investigate the clinical efficacy, safety, cost-effectiveness and predictors of response of ESI in the treatment of sciatica.

This pragmatic, multicentre, 52-week, randomised, double-blind, placebo-controlled study took place in three district hospitals and one teaching hospital in the south of England.

Subjects

All patients aged between 18 and 70 years presenting with sciatica were considered for the study subject to the following inclusion and exclusion criteria. As there was no agreed consensus on clinical practice for the use of ESIs in sciatica, several focus group discussions were held to determine best clinical practice.

Inclusion criteria

We had the following inclusion criteria:

- back pain with unilateral radicular symptoms, extending below the knee, and signs including reduced straight leg raise (SLR) and a positive sciatic nerve stretch test. The degree of SLR was determined using a protractor. A positive sciatic stretch test was defined as reproduction of sciatic symptoms on dorsiflexion of the foot when an SLR was performed
- duration of symptoms for a minimum of 4 weeks and a maximum of 18 months
- normal full blood count, erythrocyte sedimentation rate and basic bone biochemistry
- a lumbar spine X-ray to exclude other causes of radicular pain, including infection or malignancy.

Exclusion criteria

We excluded patients who had the following:

- previous back surgery
- bleeding diathesis or use of anticoagulants
- bilateral symptoms
- previous epidural injection
- current litigation relating to the sciatic symptoms or significant psychological disorders.

Participants

Patients were recruited from orthopaedic, rheumatology clinics and pain clinics in the four participating centres. A GP fast-track epidural service, seeing patients within 2 weeks of referral, was in operation at one centre. However, that service was found to have very few patients with true sciatica and so use of that clinic was abandoned.

Randomisation

Subjects were randomised to treatment or placebo group using random permuted blocks of ten. The randomisation was performed separately for each centre and was stratified for the duration of disease (less than or more than 4 months, termed acute or chronic, respectively). Randomisation was computer generated and used sealed envelopes in each centre.

Interventions

The treatment group received a lumbar epidural injection, using standard techniques, of 80 mg triamcinolone acetonide and 10 ml 0.125% bupivacaine.

The placebo received an injection of 2 ml of normal saline into the interspinous ligament with identical preparations and needles to the treatment group.

All patients had received a standardised physiotherapy package before the study, focusing mainly on education and exercise regimens. They had consumed analgesics and anti-inflammatory medicines as required.

Ethical permission was granted by local ethics committees in each of the institutions.

Figure 1 shows the study schedule. The study was carried out from 1999 to 2002. A late start at two centres led to a late completion of the trial at those centres.

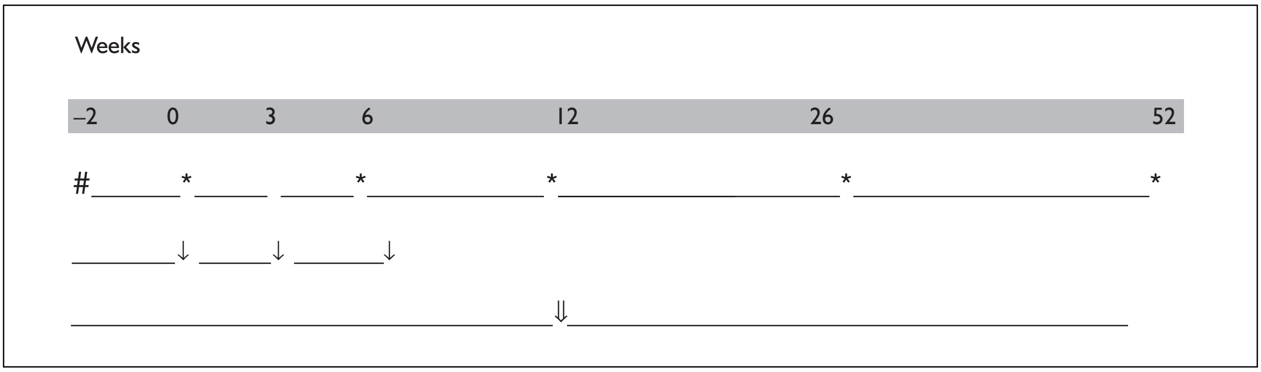

FIGURE 1 *Design of the study. #, assessment by researcher to assess eligibility; *, assessment by researcher; ↓, injections; ⇓, patients withdrawn if < 10% improvement in Oswestry Disability Questionnaire (ODQ) score from baseline.*

Subjects were assessed at 0, 3, 6, 12, 26 and 52 weeks by a trained investigator, who was blinded to the patient's treatment status. All investigators received standard training in the relevant research tools to be used and both interobserver and intraobserver reliability were tested until acceptable standards were achieved. All assistants throughout the procedure were also blinded to the content of the injection. They were instructed to put out the contents needed for both injections and then stand on the opposite side of the patient so that they were unable to see which procedure the operator chose. The operator also allowed for the fact that the placebo injection was considerably easier to perform than the active injection by taking longer over this than was necessary. The operator had no further contact with the subject. Patients and ongoing treating physicians were blinded to the injection performed.

At each visit the following were performed:

- Oswestry low back pain Disability Questionnaire (ODQ)[46]
- Short Form 36 (SF-36)[47]
- visual analogue scale for both back and radicular pain (VAS)
- McGill Pain Questionnaire (MPQ)[48]
- Hospital Anxiety and Depression Scale (HAD)[49]
- analgesic intake
- work status
- standardised objective tests of physical function[50]
- objective measures of sciatic root irritation: SLR and neurological deficit
- side-effects of the procedure.

At the end of the study patients were asked which treatment arm they thought they were in, to assess the efficacy of blinding.

Choice of outcome measures

Condition-specific health status measures are commonly used as outcome measures in clinical trials and to assess patient progress in routine clinical practice. An expert panel has recommended that, when possible, a core set of domains – back-specific measurement of function, generic health status, pain, work disability and patient satisfaction[51] – should be used. The ODQ is a recommended measure of back-specific function.[52] Established cut-offs and clinically significant change have been reported for this questionnaire. The ODQ was designed as a measure for both assessment and outcome and has been widely used in comparative studies. Therefore, the ODQ was selected as the primary outcome measure.

Among the generic measures, the SF-36 strikes the best balance among length, reliability, validity, responsiveness and experience in large populations of patients with back pain. Moreover, the SF-36 Bodily Pain scale provides a brief measure of pain intensity and pain interference with activities. Health-related work disability includes a measure of work status and work-time loss. Secondary outcome measures were, therefore: pain (VAS and MPQ), objective measure of physical function,[50] return to work, analgesic intake, surgery and neurological signs (SLR, sensory deficits and reflex changes).

Repeat injections

Injections, according to study group, were repeated at 3 and 6 weeks in relation to response. The indication for a repeat injection was less than a 75% improvement in ODQ from the baseline visit. A clinically significant change has previously been described as a 75% improvement on the

ODQ. In some centres an ESI is repeated in close proximity in time to the original injection if a small benefit is found. The choice of 75% improvement in score and up to three injections most closely mirrored local practice.

Code breaking

The patient's code was broken if either or both of the following criteria were fulfilled:

- any deterioration in neurological symptoms
- less than a 10% improvement in ODQ at 12 weeks or subsequent visits.

If the patient had received placebo injections then the patient was allowed to cross over and receive an active injection. Their data were carried forward using last observation carried forward (LOCF) from this point until 52 weeks when a final full set of data was taken.

Power calculation

The ODQ was the primary outcome measure. Its standard deviation in a population of subjects with sciatica is 15.6 points.[17] Each group needed 120 patients ($\alpha = 0.05$, $\beta = 0.1$) to give a power of 90% to detect a significant difference of 7.25 points (i.e. half a standard deviation). This figure is well below the clinically meaningful difference of 15 as recommended by Roland and Fairbank.[51] This would give ample statistical power to detect any meaningful clinically relevant treatment effect, thereby minimising the chance of inconclusive results. The study had 90% power to detect an effect size of 0.46.

An alternative method of calculating statistical power is to use a dichotomous outcome based on the ODQ. A successful outcome was defined as 75% improvement. A 75% improvement in ODQ would move any patient into the moderate or minimal disability category. For example:

ODQ score before	After 75% improvement
81–100: bedridden	20–25: moderate disability
61–80: crippled	15–20: minimal disability
41–60: severe disability	10–15: minimal disability
21–40: moderate disability	4–10: minimal disability

Assuming that 50% of the placebo arm have a successful outcome and using $\alpha = 0.05$, $\beta = 0.1$ and a dropout of 20%, a success rate of 72% would be detected in the treatment arm.

Statistics

Efficacy analysis

An intention-to-treat (ITT) analysis was performed using the ODQ as the main outcome variable. All dropouts and protocol withdrawals were contacted again by post and telephoned just before their 52-week visit to obtain updated information. Mean improvement in each group was compared by an unpaired *t*-test and by analysis of variance (ANOVA) to adjust for any poorly matched baseline characteristics. Subset analyses were performed to assess the efficacy of epidural injections in patients with acute and chronic sciatica.

An ITT basis was used so that all patients recruited into the study were included in the analysis even if they withdrew or were lost to follow-up. Patients withdrawn from the study according to protocol or for other reasons, or who were lost to follow-up, were analysed using the technique of LOCF until 52 weeks. At 52 weeks a further set of data was taken from all patients. Only those who were uncontactable at 52 weeks had data imputed using LOCF at this point.

All variables were normalised if not normally distributed. Continuous variables were analysed using ANOVA, entering baseline values as covariates and treatment as an explanatory variable. For dichotomous variables the χ^2 test was used. To examine predictors of response to treatment, such as duration of symptoms, the groups were stratified according to predictive variables and the above tests performed on each strata. If a difference appeared likely a formal interaction test was performed using logistic regression. Predictors of outcome were also analysed using logistic regression. All statistical analyses were performed using Stata Version 7.0. Analysis of surgical intervention and return to work were described using odds ratios. Numbers needed to treat (NNT) were calculated using standard methods.[53]

Health economic methods are described in Chapter 3.

Chapter 3

Economic analysis methodology

Study question

The objective of the economic analysis was to determine the additional costs of delivering ESIs for patients presenting with sciatica compared with the (additional) benefits that ESI delivers over an alternative, namely placebo.

In its simplest form, an economic analysis requires an empirical investigation of costs and outcomes to determine whether the clinical intervention is worth doing compared with the alternative treatments of the same condition. Therefore, an economic evaluation, if properly conducted, compares the relative costs of provision and the resulting outcomes of the alternatives. This enables conclusions to be drawn as to which therapy provides the maximum health benefit at the lowest costs. Hence, it prevents any conclusions that cheaper interventions of lesser quality are necessarily better.

An economic analysis can be conducted from a range of perspectives. The perspective chosen (e.g. societal, patient, purchaser or provider) will affect how costs and benefits are valued. Correspondingly, what may look viable from one perspective may not look attractive from another.

In this study, an economic analysis was undertaken for the delivery of ESIs to patients presenting with sciatica at the point of referral to secondary care. The type of economic analysis undertaken was cost–utility analysis. Costs were derived from both the providers' and the purchasers' perspectives, and quality-adjusted life-years (QALYs) were derived as a measure of utility. In this chapter, the methodology underpinning the cost–utility analysis is presented. Details on treatment of uncertainty in the economic analysis are also described.

Which costs?

An economic analysis measures the incremental difference between two alternatives. Costs that are consumed equally by both groups therefore do not need to be considered as they effectively cancel each other out. In this analysis all patients were assumed to have received a standard package of care that included physiotherapy, education and analgesia (see Appendix 2 for details). These costs were therefore not explicitly measured. Costs that were assumed to differ between the two groups included the cost of delivering an epidural injection. These costs included clinician time, medical material costs and drug use specific to the treatment. Costs that were assumed not to differ included the use of analgesics (see Appendix 2).

Derivation of providers' costs (real resource costs)

The cost from the providers' perspective was based on real resource use to determine the opportunity cost of provision. In this study resource costs were estimated as a product of standard NHS Trust costings multiplied by the units used. Resource use was estimated from data collected from the three trial centres, for the initial patient consultation, the epidural procedure and follow-up review. Resource data included:

- time taken on assessment and review by the clinician
- medical and nursing time incurred during the procedure
- nursing time on recovery postprocedure
- drug and equipment use
- pathology and radiology use.

Equipment and drugs used in the epidural injection were assumed to be one unit. Appointment times were found to be poorly representative of actual units of time expended by clinicians and nurses in managing a patient. Therefore, data were collected to determine resource use. Resource use related to shared inputs, such as clerical support and capital use (e.g. room) were not explicitly separated out for this patient group. These items were accounted for by a simple allocation adjustment based on total direct costs as advised by one Trust's financial directorate.

Cost data for clinical staff were obtained from the same financial directorate. Medical costs of the procedure (the epidural injection) were derived from a bottom–up costing approach. Overhead costs were calculated by adding 20% to direct costs, as recommended by the Trust's financial directorate. All costs are reported in 2002/03 pounds sterling. The average cost of treating a patient was estimated under two patient management strategies, representing the trial protocol and a patient management strategy practice based on the clinical trial results (one ESI). Average costs were compared across resources use between the three trial centres. Results were subject to sensitivity analysis.

Data collection on resource use

A data collection exercise was piloted to test the viability and quality of collecting data from nurses, clinicians and clerical staff across the three centres. This revealed a number of difficulties, which were addressed as follows.

- Data collected from staff seeing patients in the randomised controlled trial (RCT) were significantly distorted by data collected from staff treating patients as part of 'normal clinical practice'. For the results of the economic evaluation to be applicable to other clinical settings, data collected need to reflect as closely as possible 'normal/pragmatic practice'. It was assumed that resource use incurred by patients outside the tightly defined trial protocol would be more representative of a heterogeneous group of patients seen in normal practice. Hence, resource-use data were collected from clinicians and nurses for patients with sciatica receiving ESIs but not included in the RCT.
- Clerical staff were unable to identify, with any degree of confidence, the time spent on an individual patient. Consequently, it was agreed that resource data would be collected from medical staff only (i.e. clinicians and nurses).
- Some degree of difficulty was encountered in persuading staff of the validity of the data-collection exercise. This was largely a reflection of the fact that staff were already overburdened. This had serious implications for the viability of any survey. Consequently, it was decided to survey over a relatively short period of 3 months to ensure a high degree of participation.

Resource-use data were collected across all three centres during the period July 2000 to October 2000. Data were collected through use of a self-completion record sheet on which all clinical staff (including nurses) recorded the resources that they used inclusive of their own time. Specifically, they were asked to record time spent in consultation with the patient, aiding or assisting the patient before or after consultation, and time associated with patient administration, for all patients presenting for sciatica not included in the trial. This was under supervision of a researcher in each centre. The main costs estimated from the survey are presented in Appendix 2 (*Tables 16–25*).

Derivation of purchaser costs

Cost to purchasers (NHS recharge costs) were provided by the NHS finance directorate (Southampton Trust). Average prices charged to purchasers are based on total costs of service (including overheads).

Treatment cost per patient

The cost data were used to calculate a cost per patient for treating sciatica with epidural injections from the perspective of the healthcare provider and purchaser. It was considered appropriate to derive an average cost per patient based on two patient management practices:

- a patient management practice where the patient receives an epidural injection according to the trial protocol
- a patient management strategy where the patient receives only one epidural injection, consistent with the results of the clinical trial.

Under each management practice, it was assumed that patients had an initial consultation and follow-up. The average costs of a patient under each patient management strategy from the providers' and purchasers' perspective were derived. Given the short time horizon over which both costs and benefits are incurred, discounting was not undertaken.

Derivation of an economic outcome measure

QALYs were derived from preference-based health values (summary health utility score) using SF-36 data. The technique used is presented by Brazier and colleagues.[54]

SF-6D health state classification was derived from SF-36 raw score data. Data were checked for inconsistencies and these were corrected assuming logical consistency with reported scores at the level of the individual. Standard gambles (SGs) were calculated using Model 10.[54] SG scores were calculated assuming the trial protocol; that is, a patient would receive up to three epidural injections.

Cost–utility analysis

When allocating scarce resources to their most effective use it is necessary to compare the real resource implications of existing practice over the alternative. In a healthcare setting this requires that the additional costs are compared with the (additional) benefits delivered, and this is compared against alternatives.

The incremental ratio of cost per outcome for two treatments (A and B) is calculated as follows:

$$\frac{\text{Mean cost (A)} - \text{Mean costs (B)}}{\text{Mean outcome (A)} - \text{Mean outcome (B)}} \qquad (1)$$

In this study costs and incremental QALYs were derived and cost–utility ratios generated. The cost–utility ratio measures the incremental cost of the intervention (from a particular viewpoint) compared with the incremental health improvement of the procedure. Equation (1), expressed in terms of QALYs, becomes:

$$\frac{\text{Cost (A)} - \text{Costs (B)}}{\begin{array}{c}\text{Number of QALYs produced (A)} - \\ \text{Number of QALYs produced (B)}\end{array}} \qquad (2)$$

Incremental QALYs were derived as the difference in the area between the SG curve for the active group and placebo groups. The base for the estimation of the incremental costs and benefits was the placebo group. Given that both the active and the placebo group received a standard package of analgesics and physiotherapy the cost–utility ratio (e.g. the incremental cost per QALY) is derived for managing a patient with an ESI.

NNT to achieve a significant improvement were calculated. NNT were combined with cost data to demonstrate the total cost of realising a transient benefit at 3 weeks for one patient. Recent research has confirmed the appropriateness of using NNT in economic evaluations, given that the effect of intervention is immediate.[55]

Sensitivity and scenario analysis

Real resource costs were derived based on a set of assumptions. Sensitivity analysis was used to explore how these cost estimates change, given that the assumptions that underlay the real resource base case are relaxed. To explore an upper boundary of resource use under each of the patient management strategies, the cost per patient of each treatment was recalculated using the maximum recorded time across all three centres.

Sensitivity analysis was not undertaken for purchaser costs since these represent administratively set prices rather than real resource use. Hence, they are not subject to the type of variations that real resource costs may experience.

Chapter 4

Results

Clinical effectiveness

Forty per cent of those screened were accepted into the study. In total, 228 patients with sciatica were recruited into the study from the three centres, with 120 in the epidural group and 108 in the placebo group. The trial was halted at this stage owing to difficulties in recruitment at one centre. The power of the study more than adequately covered this shortfall. The two groups were well matched for baseline clinical characteristics (*Table 1*). Approximately one-third of the patients were acute and two-thirds chronic. The acute patients had slightly higher disability and altered neurology compared with chronic patients, although these differences were not statistically significant (*Table 2*). Ninety-one patients (40%) had had a previous episode of sciatica. One-third of patients were off work because of their sciatica. From the MPQ the incidence of items that include descriptors associated with neuropathic pain (burning pain, shooting pain, paraesthesia) was 48%, 81% and 46%, respectively.

Figure 2 shows progress through the stages of the trial according to Consolidated Standards of Reporting Trials (CONSORT) guidelines. Forty-seven per cent of patients received all three injections, 32% received two injections and 21% only one injection. The reasons for not receiving all three injections were: 60 (26.3%) owing to achieving a 75% improvement in ODQ, 55 (24.1%) owing to withdrawal per protocol (e.g. neurological deterioration) and six (2.6%) owing to non-adherence. In total, 161 patients (71%) completed all visits to 12 weeks, and 90 (40%) to week 52 without any withdrawal or cross-over. The majority of protocol withdrawals were at 12 weeks, when 24 patients from the active group and 23 patients from the placebo group withdrew owing to a lack of significant improvement in the ODQ, that is, they remained significantly disabled. There was no difference in the two groups in total dropout, protocol withdrawals or non-adherence. By 26 weeks, however, only a small number had relevant follow-up data and the majority of data had to be imputed using LOCF. The 26-week time-point data were therefore considered too small to be of relevance and were excluded from analysis. At 52 weeks, 203 patients were successfully contacted to ascertain additional treatments and their final data. Patients were also

TABLE 1 *Baseline clinical characteristics of 228 patients with sciatica*

	Active	Placebo
No. of subjects	120	108
Age (years)[a]	43 (12)	44 (12)
Height (m)[a]	1.7 (0.1)	1.7 (0.1)
Weight (kg)[a]	80 (16)	81 (18)
Gender (female %)	48.3	46.3
ODQ score[a]	44 (15)	45 (18)
VAS leg pain[a]	52 (23)	56 (22)
VAS back pain[a]	40 (24)	44 (25)
HAD anxiety[a] (cut-off = 8)	9 (3)	9 (4)
HAD depression[a] (cut–off = 8)	7 (4)	8 (4)
SF-36 total score[a]	46 (12)	46 (15)
No. of analgesics used in previous week[b]	37 (14–56)	34 (14–58)
Off work with sciatica (%)	34.2	31.5
Previous sciatica (%)	40.0	39.8
Acute (%)	38.3	35.2
Decreased sensation (%)	78.3	63.0
Absent/decreased ankle reflexes (%)	32.5	32.4
Decreased power (%)	41.7	42.6

[a] Mean (SD)
[b] Median (interquartile range).

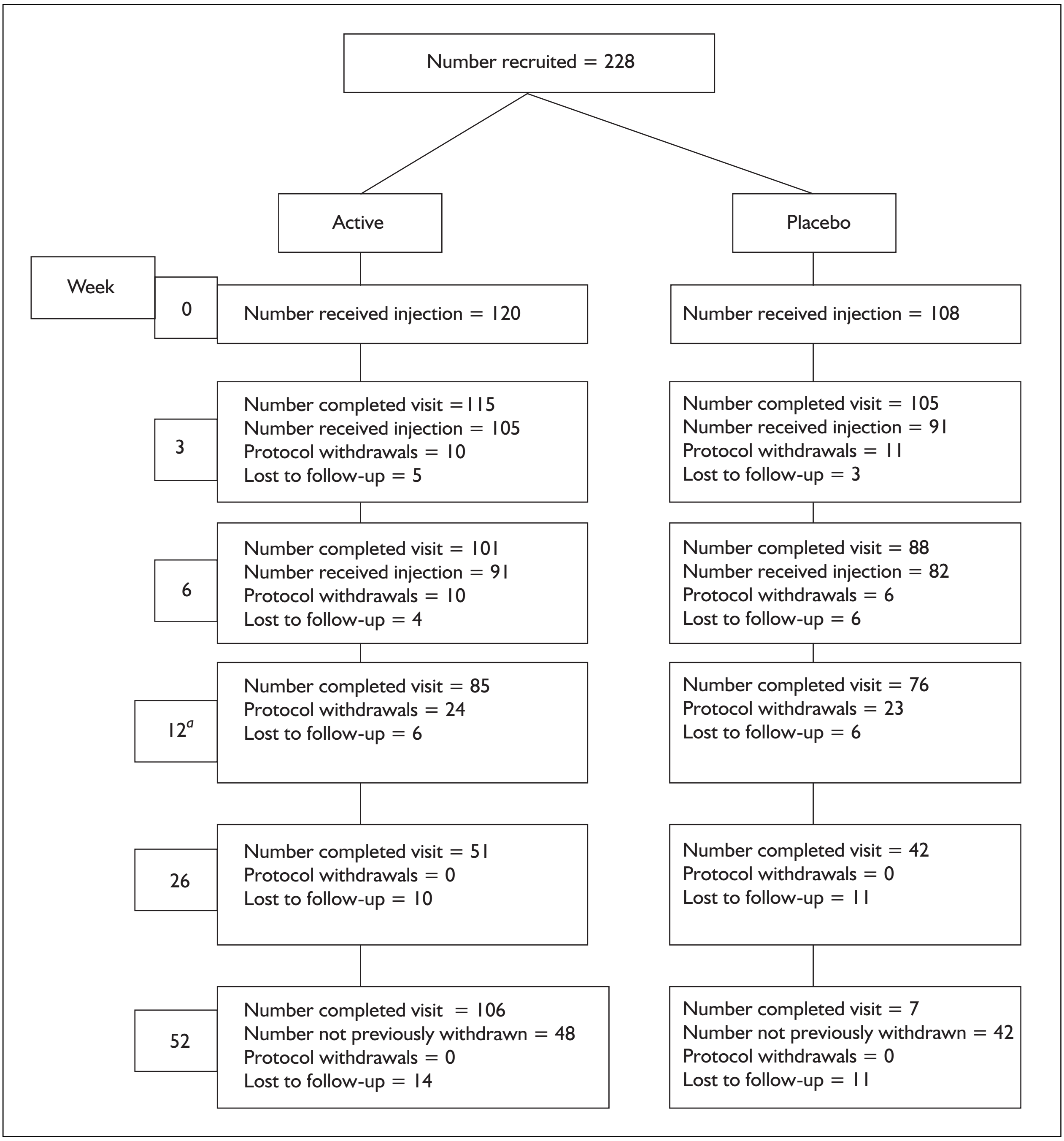
Number recruited = 228
Active
Placebo
Week
0
Number received injection = 120
Number received injection = 108
3
Number completed visit =115
Number received injection = 105
Protocol withdrawals = 10
Lost to follow-up = 5
Number completed visit = 105
Number received injection = 91
Protocol withdrawals = 11
Lost to follow-up = 3
6
Number completed visit = 101
Number received injection = 91
Protocol withdrawals = 10
Lost to follow-up = 4
Number completed visit = 88
Number received injection = 82
Protocol withdrawals = 6
Lost to follow-up = 6
12[a]
Number completed visit = 85
Protocol withdrawals = 24
Lost to follow-up = 6
Number completed visit = 76
Protocol withdrawals = 23
Lost to follow-up = 6
26
Number completed visit = 51
Protocol withdrawals = 0
Lost to follow-up = 10
Number completed visit = 42
Protocol withdrawals = 0
Lost to follow-up = 11
52
Number completed visit = 106
Number not previously withdrawn = 48
Protocol withdrawals = 0
Lost to follow-up = 14
Number completed visit = 7
Number not previously withdrawn = 42
Protocol withdrawals = 0
Lost to follow-up = 11

FIGURE 2 *Flowchart of numbers of patients at each visit and reason for dropout. [a]At this visit, if 10% improvement was observed then the code was broken, for ethical reasons.*

asked at this point which group they thought they had been assigned to; of the active group, 63 (55%) thought that they had received an epidural injection, 50 (45%) felt that they had received the placebo injection and seven did not know. Of the placebo group, 37 (39%) thought that they had had the active injection, 58 (61%) thought that they had had placebo and 13 did not know. This result was significant at $p = 0.014$ (Fisher's exact test). *Figure 3* shows the number that remained within their study group allocation, using Kaplan–Meier survival analysis. The difference between the groups in terms of survival within the study was not significant.

Functional outcomes

On the primary outcome measure, the ODQ, at 3 weeks the active group had a greater

TABLE 2 *Baseline characteristics of acute and chronic patients*

Characteristics (mean unless otherwise stated)	Acute	Chronic
Age (years)	43	44
Height (m)	1.69	1.71
Weight (kg)	78	82
Gender (female %)	52	44
ODQ score	50	41
VAS leg pain	56	53
Total HAD score	19	16
Altered dermatomal sensation (%)	79.8	66.0
Negative/decreased ankle reflexes on the sciatic side (%)	45.2	25.0
Negative/decreased ankle eversion power on the sciatic side (%)	31.0	22.9

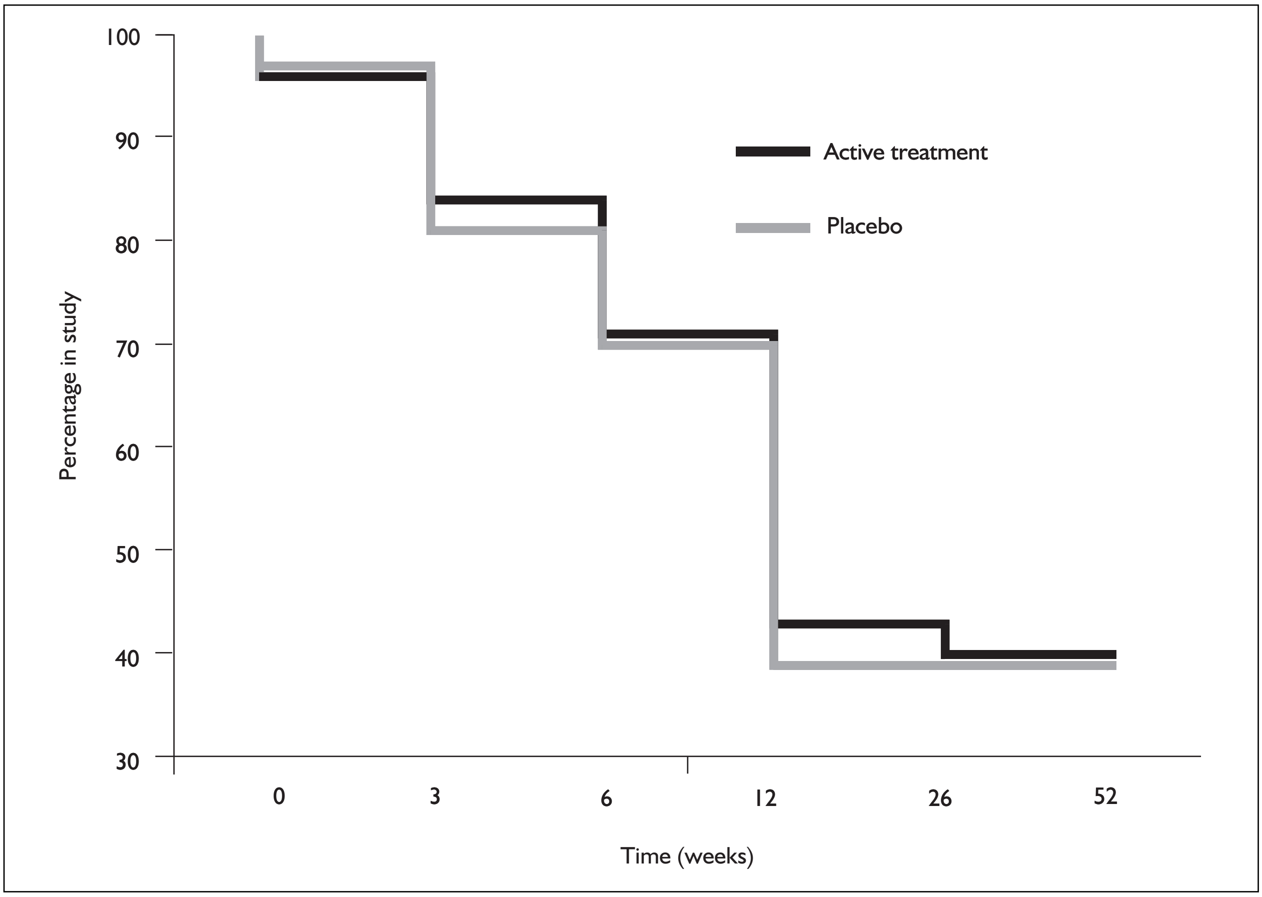

FIGURE 3 *Kaplan–Meier survival curve for study participants over the study period*

improvement in points on the ODQ than the placebo group, which was statistically significant after baseline ODQ had been accounted for [mean (SD) 10.3 (14.8) versus 6.6 (15.6), $p = 0.017$ using repeated measures ANOVA analysis taking into account all time-points] (*Table 3*). If just the 3-week time-point was used, as after that time there was no difference between groups, then the outcome of active versus placebo was not statistically significant ($p = 0.053$) (*Figure 4*). The number of patients achieving a 75% improvement in the ODQ, although small, was greater in the active group than in the placebo group [15 (12.5%) versus 4 (3.7%), $p = 0.016$] (*Figure 5*) and thus a greater number of further injections was averted in the active group. At 52 weeks, 32.5% of the active group and 29.6% of the placebo group had achieved a 75% improvement in the ODQ (*Figure 5*). The NNT to achieve a 75% improvement in ODQ by active rather than placebo injection at 3 weeks was 11.4. By 6 weeks, after a second injection, these differences had disappeared and so further

***TABLE 3** Change in ODQ in the study period (a negative score represents an improvement in disability)*

Weeks	**0**		**3**		**6**		**12**		**52**	
Group	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**
n with missing data imputed using LOCF (n^a)	120	108	120 (113)	108 (105)	120 (100)	108 (89)	120 (84)	108 (77)	120 (106)	108 (97)
	Baseline		Change from baseline							
Change in ODQ Mean (SD)	44[b] (15)	45[b] (18)	−10 (15)**	−7 (16)	−13 (17)	−10 (18)	−12 (19)	−12 (21)	−16 (23)	−14 (24)

[a] *n* represents the number with collected data at that time-point. LOCF was used at all time-points to handle missing data, to reduce bias, thus *n*= 120 for the active group and 108 for the placebo group.
[b] Baseline score.
A, active; Pl, placebo.
$^{**}p = 0.017$.

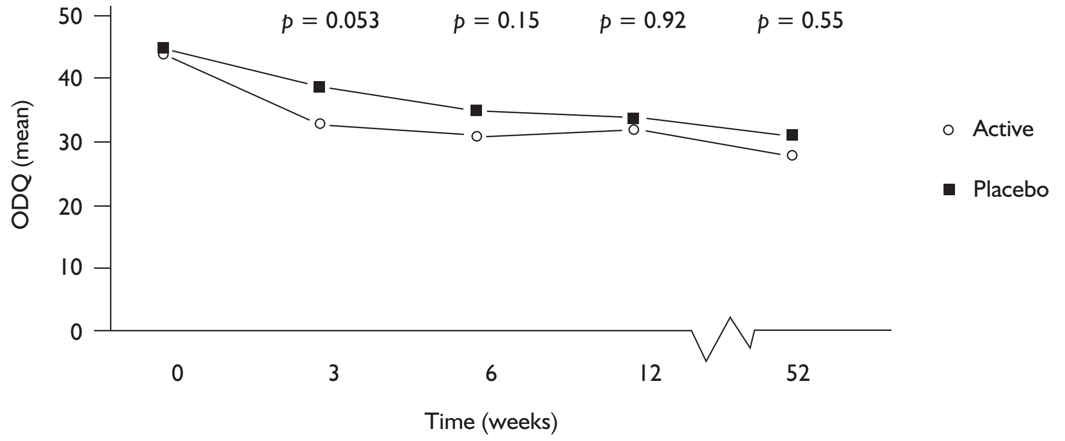

***FIGURE 4** Mean ODQ over study period, active versus placebo (p calculated for between-treatment group differences at each visit using the χ^2 test)*

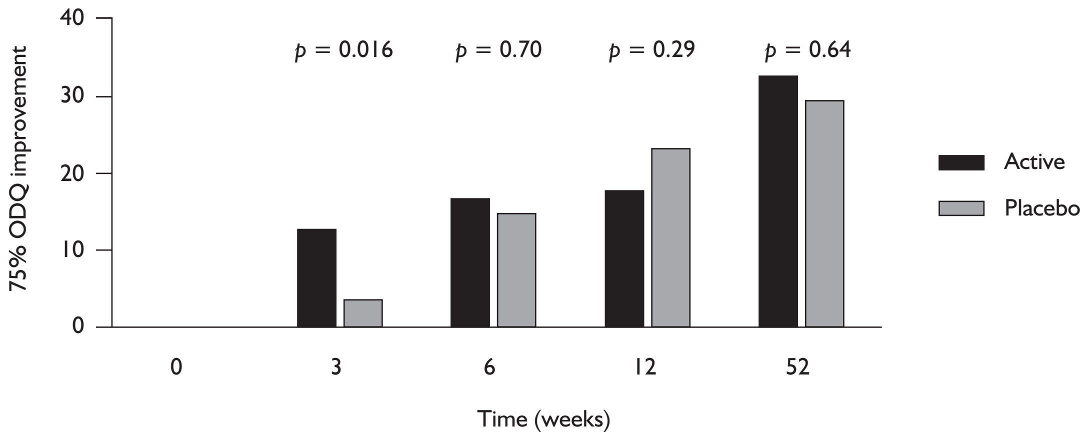

***FIGURE 5** Percentage of patients achieving a 75% improvement in ODQ by treatment group (p calculated using repeated measures ANOVA at all time-points)*

TABLE 4 *Change in objective physical measurements throughout the follow-up according to treatment group mean (standard deviation)*

Weeks	**0**		**3**		**6**		**12**		**52**	
Group	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**
n with missing data imputed using LOCF (n^a)	120	108	120 (113)	108 (105)	201 (100)	108 (89)	120 (84)	108 (77)	120 (106)	108 (97)
	Baseline		Change from baseline							
2-minute walk	84 (50)	82 (46)	6 (31)	8 (33)	8 (33)	17 (33)	9 (35)	23 (40)	13 (38)	22 (46)
1-minute stair climb	70 (30)	64 (30)	9 (22)	9 (29)	7 (28)	17 (32)	8 (29)	17 (37)	8 (33)	19 (35)
1-minute stand up/sit down	12 (7)	12 (13)	2 (4)	2 (11)	3 (11)	2 (12)	4 (13)	5 (17)	5 (17)	5 (16)

[a] *n* represents the number with collected data at that time-point. LOCF was used at all time-points to handle missing data, to reduce bias, thus $n = 120$ for the active group and 108 for the placebo group at all time-points.

TABLE 5 *Change in psychological functioning over the study period from baseline using the HAD (a negative score change indicates an improvement)*

Weeks	**0**		**3**		**6**		**12**		**52**	
Group	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**
n with missing data imputed using LOCF (n^a)	120	108	120 (113)	108 (105)	120 (100)	108 (89)	120 (84)	108 (77)	120 (106)	108 (97)
	Baseline		Change from baseline							
HAD anxiety Mean (SD)	9 (3)[b]	9 (4)[b]	–2 (3)	–2 (3)	–2 (4)	–2 (4)	–2 (4)	–3 (4)	–3 (5)	–3 (4)
HAD depression Mean (SD)	7 (4)[b]	8 (4)[b]	–1 (3)	–1 (3)	–2 (3)	–2 (4)	–2 (4)	–2 (4)	–2 (5)	–2 (5)

[a] *n* represents the number with collected data at that time-point. LOCF was used at all time-points to handle missing data, to reduce bias, thus $n = 120$ for the active group and 108 for the placebo group.
[b] Baseline value.

calculations of NNT were not done. Overall, 71/228 (31%) had a clinically significant improvement (>15 points on the ODQ) at 1 year, with no difference between active and placebo groups.

On standardised objective measures of physical function, the distance walked in 2 minutes and the number of stairs climbed in 1 minute increased throughout the period of the study, with a trend for greater improvements in the placebo group. The number of times that a patient could stand from a chair in 1 minute improved during the study equally in both treatment groups (*Table 4*). Overall quality of life, assessed using the SF-36 questionnaire, improved significantly at both 12 and 52 weeks (both $p < 0.001$); however, there were no significant differences between treatment groups. Similarly, the HAD scores decreased over the course of the study ($p < 0.001$), to a similar degree in both groups (*Table 5*), again with no significant differences between groups.

Pain

The number of patients reporting any improvement on the VAS leg pain scale [73 (61%) versus 43 (40%), $p = 0.003$ for treatment comparison] was greater at 3 weeks (*Table 7*). However, by 6 weeks this difference had disappeared [improvement on the VAS leg pain scale 68 (56.7%) versus 55 (50.9%), $p = 0.7$]. The percentage of patients achieving 50% pain relief in leg pain is shown in *Table 6*. This gives the NNT to achieve 50% leg pain relief as 11 at 3 weeks. Overall, both acute and chronic pain patients scored their back pain as being less severe than their sciatic pain on VAS at baseline [mean (SD) 42 (24) versus 54 (23)]. Back pain tended to improve throughout the duration of the trial; however, there was no difference between the two groups (*Table 6*). Other neurological symptoms and signs improved throughout the study, but there were no differences between the two treatment groups (*Table 7*).

***TABLE 6** Change in pain relief over the study period according to treatment group (a negative score indicates an improvement)*

Weeks	**0**		**3**		**6**		**12**		**52**	
Group	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**
n with missing data imputed using LOCF (n^a)	120	108	120 (113)	108 (105)	120 (100)	108 (89)	120 (84)	108 (77)	120 (106)	108 (97)
	Baseline		Change from baseline							
Continuous outcomes										
VAS mm leg pain	52	56	–12	–10	–15	–15	–13	–18	–17	–20
Mean (SD)	(23)	(22)	(28)	(28)	(32)	(32)	(33)	(33)	(36)	(34)
VAS mm back pain	40	44	–6	–2	–6	–8	–4	–7	–8	–9
Mean (SD)	(24)	(25)	(27)	(27)	(28)	(30)	(28)	(32)	(31)	(33)
Dichotomous outcomes										
% who achieved 50% leg pain relief	–	–	35	26	47	41	43	46	48	44
	Percentages who improved									
Improvement on leg pain VAS	–	–	60.8*	39.8	56.7	50.9	52.5	50.0	55.8	47.2
Improvement on back pain VAS	–	–	45.8	37.0	50.0	48.1	46.7	46.3	48.3	43.5

[a] *n* represents the number with collected data at that time-point. LOCF was used at all time-points to handle missing data, to reduce bias, thus *n* = 120 for the active group and 108 for the placebo group.

* $p < 0.01$ between active and placebo.

***TABLE 7** Percentage with positive neurological findings during the study period between groups*

Weeks	**0**		**3**		**6**		**12**		**52**	
Group	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**
n with missing data imputed using LOCF (n^a)	120	108	120 (113)	108 (105)	120 (100)	108 (89)	120 (84)	108 (77)	120 (106)	108 (97)
% Paraesthesia	45.8	40.7	34.2	38.9	29.2	38.9	26.7	31.5	21.7	30.6
% Decreased sensation	78.3	63.0	60.8	59.3	59.2	52.8	50.0	45.5	46.7	42.6
% Decreased reflex	32.5	32.4	25.8	25.9	25.0	23.2	25.8	21.3	25.8	22.2
% Reported weakness	80.0	78.7	68.3	67.6	63.3	63.0	62.5	61.1	55.8	51.9
% Decreased power	41.7	42.6	32.5	27.8	25.8	25.9	29.2	22.2	28.3	20.4

[a] *n* represents the number with collected data at that time-point. LOCF was used at all time-points to handle missing data, to reduce bias, thus *n* = 120 for the active group and 108 for the placebo group.

Other healthcare use

By the end of the 52-week follow-up period 15 patients (13%) from the active group and 14 patients (13%) from the placebo group had required surgery for their sciatica (*Table 8*). The numbers of patients in the active and placebo groups who also received the following extra therapies were: physiotherapy 31 (26%) versus 25 (23%), further epidural injections 16 (13%) versus 39 (36%), other injection techniques 16 (13%) versus 12 (11%), and pain management programme 0 (0%) versus 2 (1.9%).

Other outcomes

The number of analgesics used in the 3 weeks before the baseline visit did not differ significantly between the two treatment groups and decreased to a significant extent during the study. However, there was no significant difference between groups. Approximately one-third of all patients were not working as a result of their sciatica at entry into the study. By the end of the study this had fallen to just under one-quarter of patients, with no difference between the two treatment groups (*Table 8*).

TABLE 8 *Change in health economic outcomes over the study period*

Weeks	**0**		**3**		**6**		**12**		**52**	
Group	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**	**A**	**Pl**
n with missing data imputed using LOCF (n^a)	120	108	120 (113)	108 (105)	120 (100)	108 (89)	120 (84)	108 (77)	120 (106)	108 (97)
% off work with sciatica	34.2	31.5	34.2	29.6	30.0	28.7	27.5	24.1	24.1	22.2
	Baseline		Change from baseline (negative represents improvement)							
Days off work with sciatica Median (range)	98 (6–240)	93 (8–352)	–21 (6–240)	–21 (5–352)	–21 (6–266)	–21 (11–352)	–37 (6–266)	–23 (11–352)	–65 (6–311)	–33 (11–352)
Analgesic use (average no. consumed in a week)	37 (30)	48 (58)	–6 (23)	–11 (39)	–8 (24)	–13 (46)	–9 (25)	–16 (43)	–14 (28)	–16 (48)
					12-month data					
% who underwent surgery									12.5	13.0
% with further physiotherapy									25.8	23.2
% who had other injections									13.3	11.1

[a] *n* represents the number with collected data at that time-point. LOCF was used at all time-points to handle missing data, to reduce bias, thus *n* = 120 for the active group and 108 for the placebo group.

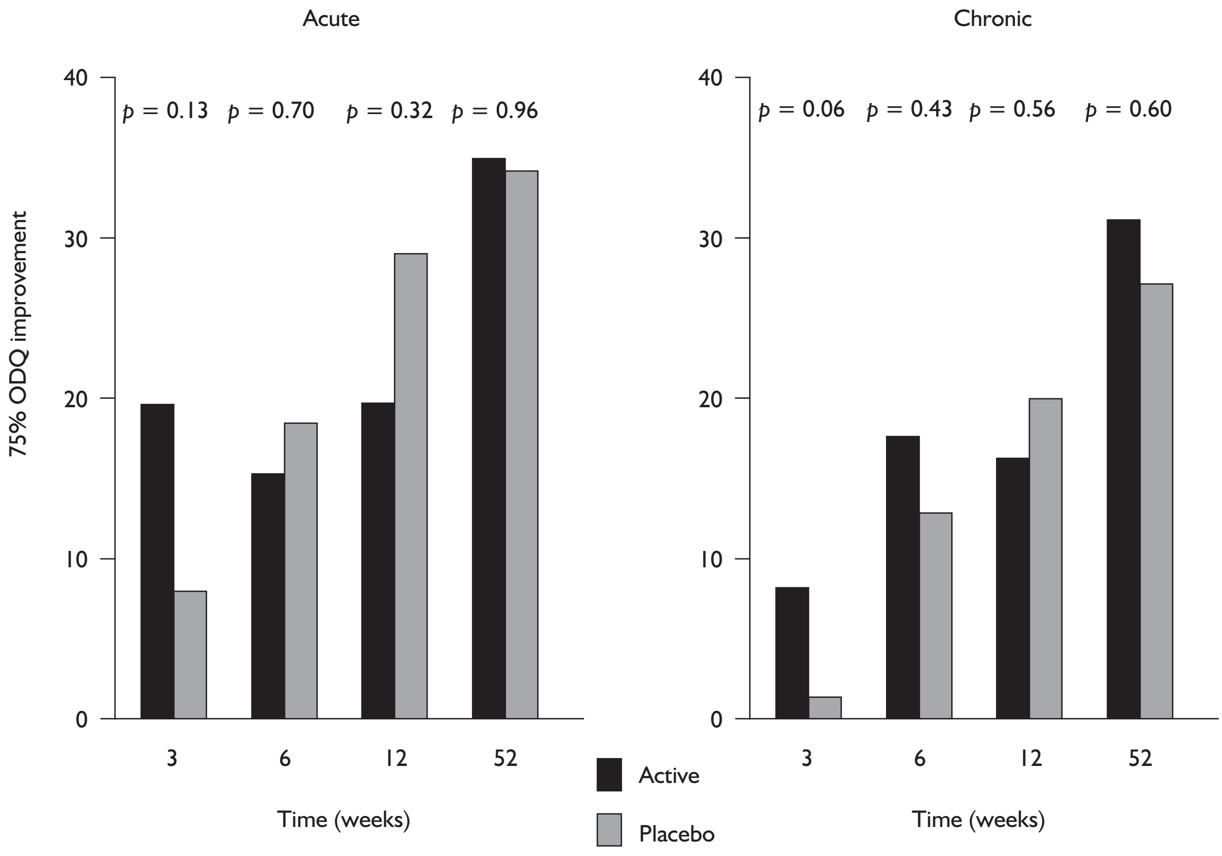

FIGURE 6 *Percentage of patients achieving a 75% improvement in ODQ by chronicity of symptoms*

Safety

There were few reported side-effects: four patients in the active group and four in the placebo group reported a non-specific headache postinjection. Other reported side-effects included PDPH (one active), nausea (two active, two placebo), and other (five active, five placebo), all of which were transient.

Predictors of response to treatment

Several baseline clinical variables were examined to explore whether they would predict groups of patients who would respond favourably to ESI. The chronic group appeared to respond better to the active injection than the acute group, but this difference was not statistically significant and not maintained (*Figure 6*). Neither the total score, anxiety or depression scales of the HAD questionnaire nor the SF-36 could identify patients likely to respond. Other variables examined and not found to predict treatment response include baseline ODQ score, neurological abnormalities (sensory loss and reflex changes), previous episodes of sciatica or back pain, onset (sudden/gradual) of sciatica, family history of sciatica, coexistent back pain, work status at baseline, gender of patient and centre.

Chapter 5

Economic results

The economic results fall into three categories: estimated costs per patient, incremental analysis of benefits from QALYs derived and cost–utility ratios. In addition, as noted in the methodology, sensitivity analysis was undertaken. The analysis was conducted for two patient management strategies: the trial protocol and a protocol based on the trial results (one epidural injection).

Estimated treatment cost per patient

The estimated average resource costs per patient treated under the two patient management strategies are presented in *Tables 9* and *10*. The estimated average resource cost per patient treated from the provider's perspective was £265.30 per patient for the trial protocol compared with £152.80 per patient assuming a management strategy based on the trial results. Average costs across the three trial centres are also presented (*Table 9*).

The determination of costs for the trial protocol was generated from resource data collected. As stated above, these data do not reflect resources expended in the trial per se, but represent the costs of applying the protocol to normal practice. Epidural costs were estimated based on 47% of patients receiving all three epidurals, 32% receiving two injections and 21% receiving only one injection. The follow-up costs were calculated assuming that each epidural received (based on the trial results) incurred this cost.

NHS recharge costs are presented in *Table 11* These are administrative costs and do not necessarily represent resources consumed. However, from the perspective of the purchaser these are the costs incurred. The average cost to purchasers of delivering treatment based on the trial design was £2102 per patient compared with £992 per patient of delivering one epidural injection based on the trial results.

Cost–utility analysis

SG scores were calculated assuming the trial protocol; that is, a patient would receive up to three epidural injections. The average SG scores at each visit are presented in *Figure 7*. However, the

TABLE 9 *Average cost per patient (£) of trial protocol (provider perspective)*

	Centre 1	Centre 2	Centre 3	Average
Review				
Pathology	20.1	20.1	20.1	20.1
Nurse time	8.2	11.5	13.6	11.1
Clinician time	15.7	23.5	25.8	21.6
Overheads	8.8	11.0	11.9	10.6
Total	52.8	66.1	71.4	63.4
Procedure				
Nurse time	57.7	35.0	40.5	44.4
Clinician time	17.2	40.8	36.0	31.3
Epidural injection	49.4	49.4	49.4	49.4
Overheads	24.9	25.0	25.2	25.0
Total	149.2	150.2	151.1	150.1
Follow-up				
Nurse time	17.2	11.9	16.5	15.2
Clinician time	44.6	21.9	17.2	27.9
Overheads	12.4	6.8	6.7	8.6
Total	74.2	40.6	40.4	51.7
Grand total	276.2	256.9	262.9	265.2

***TABLE 10** Average cost per patient (£) of management strategy based on trial results (one epidural injection) (provider perspective)*

	Centre 1	Centre 2	Centre 3	Average
Review				
Pathology	20.1	20.1	20.1	20.1
Nurse time	8.2	11.5	13.6	11.1
Clinician time	15.7	23.5	25.8	21.6
Overheads	8.8	11.0	11.9	10.6
Total	52.8	66.1	71.4	63.4
Procedure				
Nurse time	25.5	15.5	17.9	19.6
Clinician time	7.6	18.1	15.9	13.9
Epidural injection	21.9	21.9	21.9	21.9
Overheads	11.0	11.1	11.1	11.1
Total	66.0	66.6	66.8	66.5
Follow-up				
Nurse time	7.6	5.2	7.3	6.7
Clinician time	19.7	9.7	7.6	12.3
Overheads	5.5	3.0	3.0	3.8
Total	32.8	17.9	17.9	22.9
Grand total	151.6	150.6	156.1	152.7

***TABLE 11** Local trial centre and national recharge costs (purchaser perspective)*

	Local
Trial protocol	£2102
Management strategy based on trial results	£992

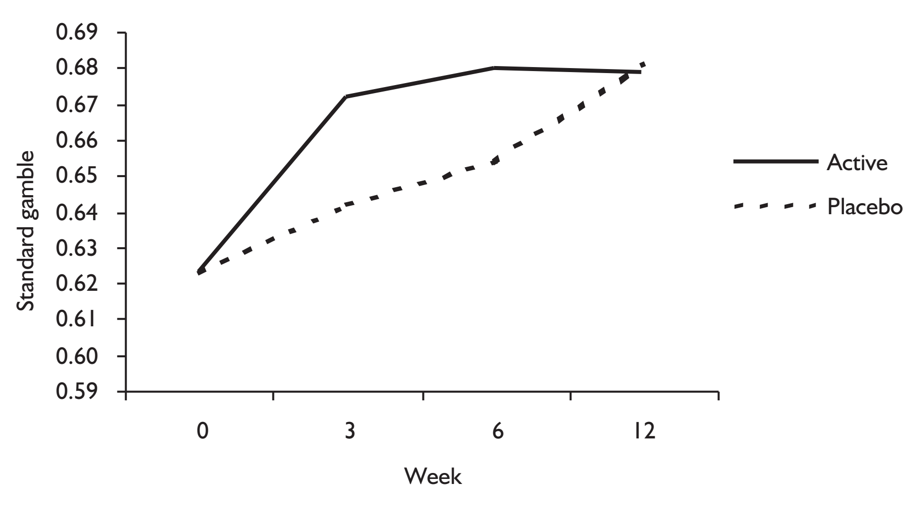

***FIGURE 7** Standard gamble uncorrected for sample population bias*

number in the sample in each period differed: week 0, active $n = 120$, placebo $n = 108$; week 3, active $n = 113$, placebo $n = 105$; week 6, active $n = 101$, placebo $n = 88$; and week 12, active $n = 85$, placebo $n = 76$. As part of the change in scores may reflect the change in the sample structure rather than average outcome, comparing these averages is potentially misleading. In *Figure 8*, average SG scores are derived for a subset of patients with observations for all visits up to week 12 (active $n = 85$, placebo $n = 76$). In both *Figures* 7 and *8* data were normalised to ensure an

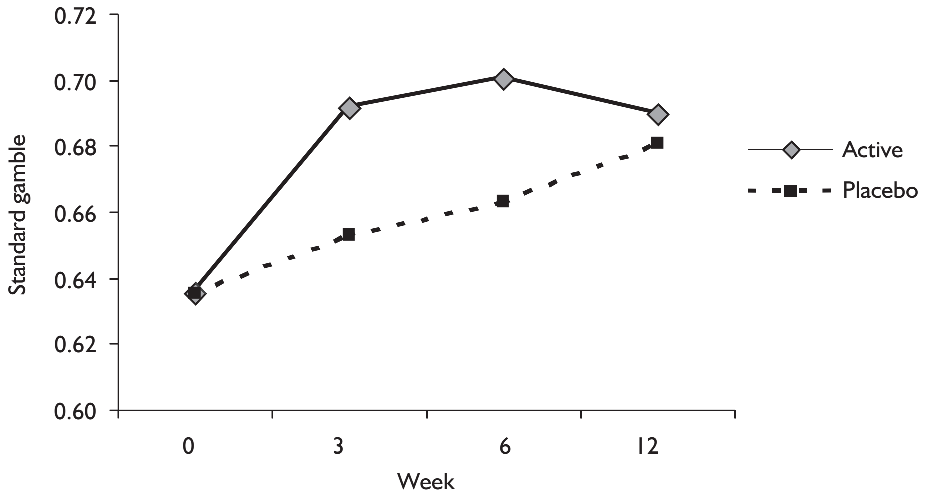

FIGURE 8 *Standard gamble corrected for sample population bias*

TABLE 12 *Incremental analysis of alternative patient management strategies*

	Trial protocol (up to three ESIs)	**Strategy based on trial results (one ESI)**
Provider perspective		
Incremental cost (£)	265.30	152.80
Incremental QALY	0.0059350	
Cost per benefit gain (£)	44,701.11	25,745.68
Purchaser perspective		
Incremental cost (£)	2102	992
Cost per benefit gain (£)	354,171.65	167,144.76

equal starting point in week 0. In week 12, average SG scores for active and placebo converged. This is consistent with what was observed in the hard clinical outcome measure (ODQ). In other words, the health gain for the active group as measured by SG was achieved by the placebo group by week 12.

Incremental QALYs were derived as the difference in the area between the SG curve for the active group and placebo group. This area was calculated from *Figure 8*. The incremental QALY gained for a patient under the trial protocol compared with the standard care package was 0.0059350. This is equivalent to an additional 2.2 days of full health.

Cost per QALY gained of ESIs over a standardised physiotherapy package were derived for both the trial protocol and a protocol based on the trial results (one epidural injection) (*Table 12*). The cost per QALY gained from the provider's perspective assuming that a patient is managed under the trial protocol was £44,701. The cost per QALY gained to the provider from a patient management strategy administering one epidural was £25,745.68 (*Table 12*). This result was derived assuming that the gain in QALY data calculated for patients under the trial protocol would approximate that under a patient management strategy based on the trial results (one ESI). This is not considered an unreasonable assumption as the change in SG scores after week 3 was lower in the active group than in the placebo group. An insufficient number of patients was treated with just one injection to confirm this from the clinical data (i.e. only 21 patients received just one injection).

The costs per QALY gained from the perspective of the purchaser are also presented (*Table 12*). The costs per QALY gained from the trial protocol and the protocol based on the trial results are £354,171.65 and £167,144.76, respectively. In both purchaser and provider

TABLE 13 *UK cost (£) of delivering sciatic injections, 2002/03 (£)*

	Provider		Purchaser	
	Trial protocol	**Management strategy based on trial results**	**Trial protocol**	**Management strategy based on trial results**
Average patient cost	265.30	152.80	2102	992
Total cost	3,945,011	2,272,136	31,256,740	14,751,040

cases these figures exceed the implied QALY thresholds (£20,000–30,000) in National Institute for Health and Clinical Excellence (NICE) technology appraisal.[56]

Costs derived using NNT

The NNT to realise a 75% improvement at 3 weeks compared with the placebo was 11.4. In these analyses, ESI was compared with a placebo injection, rather than with usual clinical care, which may falsely increase the NNT and hence costs. If all improvement at 3 weeks in the placebo group is assumed to be due to a placebo response, the NNT is reduced to 8. In reality, the real NNT figure will be between these two extremes (i.e. 8–11.4). The charge to purchasers for realising an improvement at 3 weeks in one patient based on the trial protocol is £16,816–23,963 depending on the NNT assumed (8–11.4). If only one epidural is provided, the total charge to purchasers to improve one patient at 3 weeks is £7936–11,306.

Potential cost savings

The results of the clinical trial were that epidural injections did offer a transient benefit over the placebo at 3 weeks. However, in the medium to long term (6 weeks to 12 months), there was no benefit of epidural injection over placebo injections. Consequently, the additional costs of providing more than one epidural are not offset by any significant health benefits (as measured by the primary health outcome). Adopting a patient management strategy based on the trial results would save resources compared with clinical practice according to the trial protocol. This would incur a resource cost saving of £1110 per patient from the purchaser's perspective.

It is estimated that 14,870 ESIs were performed in 2002/03.[10] The total costs of delivering 14,870 sciatica injections based on the cost data estimated in the study are presented in *Table 13*. Assuming that every patient is treated according to the trial protocol, the UK cost of delivering sciatica injections from the perspective of the provider is £3,945,011. Purchasers spent £31,256,740. Reducing this to one epidural injection to realise the transient benefits would be a saving of £16,505,700 to purchasers.

Other costs

Costs associated with a standardised physiotherapy package (focusing mainly on education and exercise regimens) were not considered as these patient costs would be incurred regardless of whether a patient presenting with sciatica received an epidural or not.

Although there was an apparent difference in analgesic use between the two groups (*Table 8*), this was not statistically significant. This indicates that there was a large variation in use in both groups. The apparent difference occurred even before the trial (i.e. week 0). Normalising the analgesic use to look at changes in use results in similar patterns between the two groups (*Figure 9*). As a result, differences in analgesic use were not considered a consequence of the treatments, just an artefact of the sample. Analgesic costs therefore were assumed not to differ between the two groups and therefore not considered in the economic analysis.

Costs associated with radiology and pathology were incurred after the initial review if not already performed by the referring source. These costs were reported as £18 and £2.10, respectively, from the finance directorate. Health service utilisation after week 52, specifically surgery, other injections and further physiotherapy, was recorded, but no significant difference was found between the two groups (see *Table 8*). Consequently, the costs of these were not included in the economic analysis.

Other costs incurred by patients, e.g. an overnight stay (£75), were included in the sensitivity analysis.

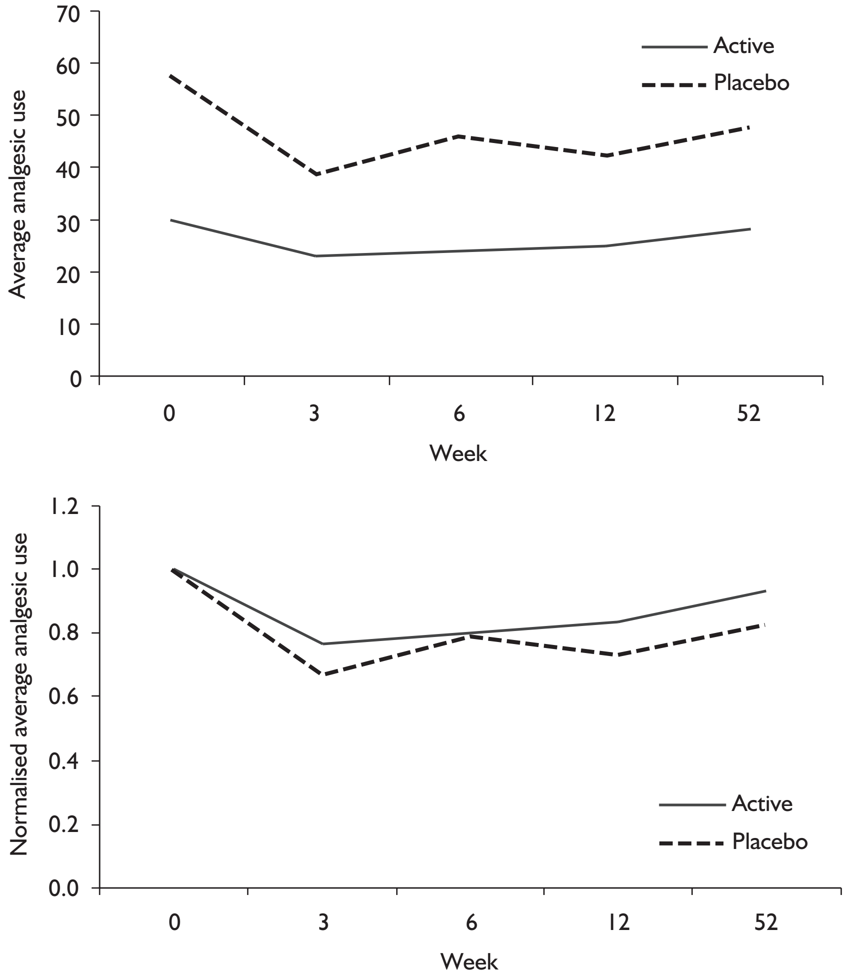

FIGURE 9 *Average and normalised analgesic use*

Overhead costs

Overhead costs were calculated based on adding 20% to direct costs. This was as advised by the financial directorate of one Trust. Administration other than that undertaken by nurse and clinicians was assumed to be negligible, so their costs were not included. Effectively, it was assumed that there would be no administrative resource savings from the perspective of the Trust by not treating these patients. (The hourly cost of administration and clerical support ranged between £6.88 and £8.38. If it is assumed that each patient uses 5 minutes of administration, this adds between 55 and 67 pence per patient to the average patient cost.)

Sensitivity analysis

Sensitivity analysis was undertaken on key input parameters to demonstrate how costs would change given a relaxation in the base-case assumptions. Labour time accounts for over 50% of the total costs. Variation in labour practices was observed between the three trial centres and the costs of running each management strategy in these centres are presented in *Tables 9* and *10*. To explore an upper boundary of resource use under each of the patient management strategies, the cost analysis was recalculated using the maximum recorded time across all three centres. The results are presented in *Table 14*. Assuming maximum recorded time for nurses and clinicians more than doubles the average patient cost under each management strategy.

An implicit assumption of the base-case analysis was that a patient attends as a day case. An overnight stay incurs an additional cost of £75. The average costs under each patient management strategy requiring an overnight stay are presented in *Table 15*. Changing this assumption has the

TABLE 14 *Maximum cost per patient (£)*

	Trial protocol		Management strategy based on trial results	
	Base case	**Maximum resource use**	**Base case**	**Maximum resource use**
Review				
Pathology	20.1	20.1	20.1	20.1
Nurse time	11.1	33.7	11.1	33.7
Clinician time	21.6	36.6	21.6	36.6
Overheads	10.6	18.1	10.6	18.1
Total	63.4	88.4	63.4	88.4
Procedure				
Nurse time	19.6	203.9	44.4	90.2
Clinician time	13.9	140.2	31.3	62.0
Epidural injection	21.9	49.4	49.4	21.9
Overheads	11.1	78.7	25.0	34.8
Total	66.5	472.2	150.2	208.9
Follow-up				
Nurse time	6.7	30.5	15.2	13.5
Clinician time	12.3	70.1	27.9	31.0
Overheads	3.8	20.1	8.6	8.9
Total	22.9	120.7	51.7	53.4
Grand total	152.8	681.3	265.3	350.7

TABLE 15 *Average patient costs (£) assuming overnight stay required*

	Trial protocol	Management strategy based on trial results
Bournemouth	479.60	241.60
Portsmouth	460.30	240.50
Southampton	466.40	246.20
Average	468.70	242.80

effect of increasing costs under both patient management strategies. The scenario under which these average patient costs were derived assumed that the patient was required to stay after an epidural. This is an extreme assumption, as it would be reasonable to assume some mix of day patients and those requiring an overnight stay. The real resource cost therefore lies somewhere between this value and those presented in *Tables 9* and *10*. (No patients were recorded as requiring an overnight stay during the survey period.) In both cases the above costs increase. Assuming that QALYs remained unchanged, the effect would be to increase the cost–utility ratio further.

Chapter 6

Analysis of robustness of results

This study is the largest study of its kind and rates more highly than others, based on criteria that are generally accepted as principles of intervention research.[57] The results confirm that although epidural injections of corticosteroids may offer limited short-term relief of symptoms in patients with sciatica, they offer no medium- or long-term benefit. An additional 9% of patients achieved the predefined response criteria at 3 weeks compared with placebo, but by 6 weeks this additional benefit had all but disappeared. In addition, ESIs do not hasten return to work, reduce the use of other health facilities or prevent the need for surgery.

This was a pragmatic study of epidural corticosteroid injections and as such was performed to mirror and assess current clinical practice. Patients were therefore selected on clinical grounds and an attempt was made to include all patients passing through the hospital service. The patients recruited were very similar in terms of pain scores and neurological compromise to those in other studies that used cross-sectional imaging in their inclusion criteria.[16,18] The mean baseline ODQ score in the present patients of 44 is classed as moderate disability. The authors are confident that the patients recruited included the full range of severity of sciatica from relatively mild to severe.There is no consensus among clinicians as to best practice for the use of ESIs. In a recent survey methylprednisolone was the most commonly used steroid (42%); alternatives included triamcinolone (38%) and hydrocortisone in combination with methylprednisolone (20%). Bupivacaine was the most commonly used local anaesthetic (bupivacaine 67% : lignocaine 33%).[58]

The effectiveness of ESI is difficult to interpret from previous studies owing to marked heterogeneity in their study design. The results have varied markedly in their ability to reduce pain, with several studies showing no benefit and others demonstrating significant benefit.[14–21,23] Many of these studies were small, and used different patient populations and different approaches to the epidural space, but most importantly assessed outcome at different time-points. Two negative studies used 24 hours as an outcome time.[18,19] This is probably too early to detect an effect. Other positive studies had short- to medium-term follow-up periods.[14,15,17,21] This study, being the first to follow patients regularly from 3 weeks to 52 weeks, helps to clarify the situation. Epidural corticosteroids can lead to a modest improvement in pain and disability at 3 weeks, but by 6 weeks and through to 52 weeks they are no more effective than placebo injections.

Only 90 patients completed the study to week 52. The majority of patients failed to reach this time-point as they had reached protocol end-points owing to withdrawal because they had either deteriorated within 12 weeks or failed to improve significantly by 12 or 26 weeks. As such, this group had complete end-point data for statistical analysis using the LOCF technique. Only 54 patients (24%) were lost to follow-up, as predicted in the initial power calculation. The high number of protocol withdrawals was unexpected. If patients had not shown any improvement in the first few weeks after injection it was highly likely that no further improvement would be forthcoming. The majority of protocol withdrawals occurred at 12 weeks, when failure to improve by more than 10% necessitated withdrawal for ethical reasons. There was no difference between placebo and active groups in this. Thus, there was a significant amount of missing data by 12 weeks, mainly due to failure of the technique. LOCF was used to manage these missing data up to the final follow-up. LOCF is recommended as a way of handling missing data in ITT analyses.[59] However, as there were so many dropouts and protocol withdrawals after the 3-month visit a decision was made to look only at long-term follow-up data after this point. Complete case analysis (i.e. only including the actual data recorded) would have led to bias unless the data were missing at random, that is, absence of an observation is independent of the outcome. Partial information, such as outcome at some time-points, or time to dropout, may be used to produce a more efficient analysis, but this is still potentially biased. Thus, it was felt that LOCF would produce the least biased results. The vast majority of patients (211) were contacted at 12 months and complete data were taken on 203 patients at that point, including additional treatments since withdrawal. This was important to establish as, in true practice, ESIs are seen as a relatively low-cost, conservative option and are often tried in an attempt to avert more costly, complex treatments. Whether these treatments were averted was an important study outcome. ESIs appear to fail in this regard. All data collected at 12 months were true data, such as return to work and surgery. Patients who were withdrawn reached a formal study end-point and for ethical purposes had their study code broken. They were, however, still actively followed up as part of the trial to collect important secondary outcome measures and thus not formally censored.

In any RCT it is preferable to have complete double blinding to reduce bias. In this study, complete blinding of the assessor was achieved; however, as with any interventional study it is difficult to blind the subject completely. This was formally assessed at the end of the study and although not perfect the blinding appeared adequate. The bias that may have resulted from the placebo group more correctly identifying their treatment allocation than the active group would have enhanced the treatment effect, which it did not.

The Federal Drug Agency in the USA has recommended that a clinically meaningful reduction in ODQ equates to a minimum of a four-point change to 15 points. The Carette study suggested this equated to one standard deviation of change, a change that has also been recommended by Turk.[16,60] How much change is necessary on the ODQ to achieve economic gains (e.g. decreased analgesic use, decreased healthcare use) is unknown and warrants further investigation. As a significant reduction might be necessary to achieve cost-effectiveness, the upper limit of 15 points or a 75% reduction in ODQ was chosen. This also had the effect of converting all patients into mild or moderate disability, as discussed above.

In addition to assessing the overall effectiveness of a treatment, it is equally important to identify predictors of response, to define subsets of patients who may respond particularly well to the treatment. There were reasons to suspect that ESIs may be more effective in patients with acute than with chronic sciatica. In the acute stages the nerve root is often inflamed and oedematous, which may be amenable to modification by corticosteroids.[61] In chronic sciatica, however, it is likely that there is less inflammation and more perineural fibrosis, making it less likely to respond to corticosteroids. Although the patients in the acute group generally fared better than those in the chronic group, there was no difference in the effect of ESIs between the two groups. The study was underpowered to detect a difference in subgroups. Subgroup analysis was really not appropriate given that there was no clear effect of ESIs beyond 3 weeks. In addition, given the broad remit of the study, to include all patients with sciatica who may receive an ESI, and that the response overall was small and short lived, it is hardly surprising that there were no predictors of success. As the main outcome was a disability measure, more precise measurement of psychosocial predictors of disability may have been more successful. The ‘yellow flags’ approach to back pain has proved highly successful in predicting those at risk of long-term disability.[62] In particular, fear avoidance and catastrophising have been investigated.[63,64] Less was known about these factors at the time of the study and they have not been evaluated in sciatica.

The results did not indicate frequent side-effects to ESIs and thus they appear relatively safe. However, the number who received ESIs was relatively small (120 patients) and the operators were all very experienced. The incidence of major complications was zero. A much larger study would be needed to pick up such rarer complications and would be best suited to a longitudinal study.

Although it is recognised that significant indirect cost savings would be generated with successful pain relief by enabling patients to return to work, these were not considered as collection of such costs would be based on a number of assumptions, most specifically that the patient population would return to employment. Although return to work would be the most appropriate outcome measure, it was not considered as there are inherent difficulties in its definition and collection in a population of mixed age, gender and socioeconomic groups. This study did not demonstrate that ESIs altered return to work outcomes at any point and thus further analysis of this important indicator was not undertaken. There was a danger that inclusion of indirect costs would have significantly overstated potential cost savings. In addition, it is argued that indirect cost savings are irrelevant in resource allocation decisions.[50] It is well known that there are many risk factors associated with chronic work disability that may be more important than the level of pain. Without knowledge of a patient’s work satisfaction, stress, working conditions, day-to-day work demands, employer’s attitudes, and so on, this result cannot be interpreted with any degree of certainty.[65]

The UK NHS uses an internal market for charging for medical treatments. The charge levied on the purchaser therefore differs from the actual resource cost incurred. In addition, healthcare can be purchased from the private sector. Although these charges are not true resource costs, from an economic perspective, they are the financial resources expended by the purchaser and therefore have an opportunity cost equivalent to this level. These costs are very substantial for a short period of pain relief. Real resource costs were also estimated. These reflect the opportunity cost of resource use from the perspective of the provider. Therefore, the cost analysis presented addresses the lack of accurate cost data with respect to this treatment from both perspectives.

The results of the clinical trial indicated only a transient benefit of the procedure, with the benefit disappearing at 6 weeks.

The benefits to the individual from injection are seen as 2.2 days of full health. This study measured the cost-effectiveness from the provider's and the purchaser's perspective, but not from an individual perspective. The small chance of short-term pain relief (1 in 8 to 1 in 11, based on NNT calculations) compared with no pain relief may seem very attractive from an individual's perspective. Certainly, some may wish to pay for this privilege, as discussed above. However, without true safety data, which this study was unable to collect with any degree of certainty, it is hard for patients to make an informed choice.

Chapter 7

Discussion

From this study ESIs have been shown to provide significant improvement in function (>75%) compared with placebo for 3 weeks, reaching an NNT of 11.5 over placebo. This led to 2.2 days of full health compared with placebo. The study also found that lumbar ESIs offered no long-term benefit over placebo injections. They appear relatively safe. There was no advantage in performing more than one epidural as, at 6 weeks and for the remainder of the study, there were no significant differences between the groups on any measured parameter. ESIs did not avert surgery.

This study is one of many on the subject. Systematic reviews have reached discordant conclusions despite using similar data. The reasons for this have been discussed at length by Hopayian,[66] who suggests that a large, rigorous trial provides better evidence than a non-credible meta-analysis. The present trial has to be given substantial weighting compared with other studies: it has the largest number of participants, has a long duration of follow-up and includes a cost-effectiveness analysis.

Clinical effectiveness

Unlike in many other studies, there was no confusion between back pain and sciatica, although all of the patients reported back pain as well as sciatica. All patients had sciatica as defined by International Association for the Study of Pain (IASP). Indeed, 60% of patients screened were excluded, many on the grounds that they did not have true sciatica. This suggests that either the nerve root pain had disappeared by the time they came for the epidural (unlikely as the waiting time was very short) or true sciatica is poorly diagnosed. This has implications for epidemiological research. This finding is in agreement with the IASP's suggestion that the term sciatica should not be used as it is liable to misinterpretation.[67]

Before further evaluating the clinical effectiveness of ESIs it is worth discussing the size of the problem. Sciatica is a symptom commonly associated with intervertebral disc pathology. It is largely felt to be a self-limiting process that improves with conservative treatment.[1] However, the evidence from the current study is that this is not the case. Many of the patients had had sciatica for up to 18 months. Chronic pain is normally diagnosed when pain has been present beyond 3 months, so nearly all had chronic disease. Forty per cent had experienced sciatica on other occasions, indicating that in this group many of the patients had recurrent disease. At the end of the study most patients still had both back pain and leg pain, although to a lesser degree. The leg pain component was still greater than the back pain. This sample was similar to that in a previous similar study.[16] The present cohort had a mean ODQ of 44, which is similar to that in Carette's study, where the ODQ was 49, suggesting moderate disability. It must be remembered that this was a pragmatic study. The cohort case-mix was representative of those patients normally presenting as candidates for epidural injections.

These results are similar to those of other studies. In a calculation from the meta-analysis by Watts and Silagy,[23] Moore found that the NNT to achieve greater than 50% pain relief in the long term was 13.[24] In the same review, in 11 trials of short-term relief the NNT for greater than 75% pain relief in the short term (1–60 days) was 7.3. The present trial only had significance at 3 weeks. The NNT for short term 50% pain relief compared with placebo was 11.1 which compares favourably with the meta-analysis. If all the improvements at 3 weeks in the placebo group are assumed to be a placebo effect and not the natural history of sciatica, then the NNT in a real situation is reduced to 8. The real NNT will be between these two values. The pooled meta-analysis may have had poor data acquired from small clinical trials that may have skewed the outcomes to be positive, that is, reduced the NNT.[24] This could account for the apparently higher NNT in the present study. Alternatively, it could be that the patients in this group were more chronic and more disabled than in many other studies. This was not well assessed in some of the early studies.

There is some evidence to suggest that the increased clinical attention generated by entering a clinical trial alone is sufficient to evoke an improvement in patients' well-being.[69] This therefore would benefit both the placebo patients and the active group. Placebos have been previously demonstrated to have a powerful sustained effect.[70,71] It is likely that the patients in the present placebo group experienced a similar, strong placebo effect. It has been suggested that the placebo effect be used as a therapeutic tool.[72] Although this topic lies beyond the scope of this discussion, clearly the placebo group cannot be considered as a 'no treatment' group. Although a 'do nothing' option was considered, it was considered unethical by the study group and local clinicians to withhold treatment for potentially up to 1 year.

A large number of patients had shooting pain suggesting neuropathic pain. It is well established that patients with neuropathic pain have structural changes within the CNS. These changes lead to sensitisation to pain perception. Once these changes have occurred they quickly become persistent, resulting in long-term pain that can be difficult to manage, together with long-term disability. Treatment focusing on the pain alone at this stage is often inadequate and has implications for healthcare. This was the presentation of patients in this study. Sciatica that presents to secondary care therefore is a chronic disease for many people.

Consideration needs to be given as to what triggers patients to seek medical help. In the case of low back pain, a community survey found that only 50% had sought medical treatment over a 12-month period.[73] It is unclear whether this is the same for sciatica. Perhaps the patients who seek help are those who are not making any sufficient clinical progress, and this may or may not have been the case with the present study patients. Perhaps these patients were those who were not coping with their pain. It may be that pain of a neuropathic nature is more difficult to tolerate or gives rise to more alarm in patients. If there is numbness or weakness they may be more likely to seek advice early. This requires investigation.

Factors that may contribute to chronicity must be understood in order to interpret fully the clinical outcome from ESIs in this study. The need to seek help for chronic symptoms is not well explored in sciatica. In general, it is recognised that there are psychosocial issues to be considered when assessing outcome from pain therapies. Fear avoidance and catastrophising are both associated with treatment failure and subsequent chronicity.[74] The present study examined some psychosocial predictors of disability. The HAD, SF-36 and the MPQ measure psychological well-being to some extent. These measures all improved over the duration of the trial, but they did not predict outcome as assessed by the ODQ or VAS. These psychological tools were probably not sensitive enough to evaluate fear avoidance or catastrophic thinking. Other scoring systems may have been more helpful (e.g. Tampa Scale of Kinesiophobia, Fear Avoidance Beliefs Questionnaire, Pain Catastrophising Scale) and may be a better measure of cognitive content. These factors were less well recognised at the time of the inception of the study and such tools were not available. In addition, sciatica-specific measures such as the Maine–Seattle back questionnaire were not developed at the time, but again could be used now, although less is known of their clinical meaningfulness.[75]

On admission to the trial many patients had severe sciatica. They had high pain, HAD and ODQ scores. Optimal analgesic regimens for patients with sciatica have not been established. Analgesic intake was not standardised in this study. The short period of effective analgesia provided by the ESIs could be used as a window of opportunity to implement adjuvant therapies such as better analgesia and rehabilitation. However, little improvement in function resulted from this window of opportunity afforded by temporary pain relief, despite review by a pain physician to ensure that optimal analgesia and physical therapy techniques had been achieved. There is a risk that a patient will attempt rapid physical reconditioning. This was a group of patients who had been classified as having moderate to severe disability and persistent pain. Overactivity/underactivity cycling is a common pattern of activity found in this population and can lead to worsening pain and disability if not managed well. They therefore run the risk of flare-ups and deterioration again soon afterwards. This appears to have been the case in this trial. Pacing (activity scheduling) was not emphasised as part of the trial. This forms part of a standard pain rehabilitation approach as used by specialist pain physiotherapists or as part of a pain management programme where cognitive behavioural therapy (CBT) is used to effect change in pain management skills. Use of this sort of approach, which has a good evidence base to support it, may have helped considerably in improving disability and deserves further investigation.[76] Hasenbring and colleagues reported good results from individual CBT at an early stage in sciatica patients deemed to be at high risk of chronicity in terms of pain relief and improvement in function, although total therapist hours were high at 27.[77]

Many pain units (including two of the centres in this study) struggle to provide a comprehensive CBT and rehabilitation/physiotherapy programme because of gross underfunding and staff shortages. The provision of these treatments is likely to improve outcomes significantly. Severity of psychophysical functioning would determine the need for both of these services, but both would seem mandatory in this study population.

Jamison and Vade Boncceur Ferrante evaluated satisfaction in a series of 249 patients suffering with sciatica.[34] One year after a single epidural injection 63% found it helpful. With the increasing emphasis on patient centred-care it is very important to evaluate the patients' degree of satisfaction with their treatment and outcome. Jamison and co-authors also found that higher rates of satisfaction are found with treatments focusing on improving mental and physical well-being.[78] Such an approach was less well recognised as an important issue at the inception of this study, but needs to be considered in any future study design.

The data from this study demonstrated that ESI did not reduce the need for surgery, nor did it reduce the need for any other interventions, including physiotherapy, pain management programmes or other injection techniques. The number of patients requiring surgery in this study was the same in both groups and consistent with previous studies of sciatica.[21] The rates were understandably higher than those seen in Weber's study, which followed acute patients with symptoms of less than 2 weeks' duration.[79] Surgical discectomy for carefully selected patients with sciatica due to lumbar disc prolapse provides faster relief from the acute attack than conservative management, although any positive or negative effects on the lifetime natural history of the underlying disc disease are unclear. There is an increased risk of repeated surgery after one operation has been performed. In older patients and in repeated surgery the complications rise significantly. Approximately 2000 cases of 'failed back surgery syndrome' are reported each year in the UK.[80] This syndrome incorporates complications of other forms of back surgery, but is an important, serious, expensive and debilitating problem. ESIs should not, therefore, be used as a means of deferring surgery. However, the place of surgery in this cohort of patients remains unclear.

A lumbar approach to ESI is highly likely to be successful in terms of placement in the correct space. However, in cadavers it has been shown that epidural injectates flow freely within the epidural space and are directed into the lateral recesses and surround the nerve roots.[81] There are doubts about whether the steroid reaches the affected nerve root and in adequate quantities.[82] It has been shown that when blindly placed the actual level of placement is often higher.[83] Many doctors have therefore abandoned lumbar ESIs in favour of foraminal or nerve root injections, first described in the 1970s.[84] The number responding favourably may have been better using a transforaminal approach. It is unclear whether transforaminal injections are more effective than ESIs. Some evidence suggests that they may reduce the need for surgery and that they are successful in cases of lumbar radiculopathy.[85,86] However, other evidence suggests similar outcomes to blind lumbar ESIs.[87,88] Transforaminal injections are more complex to perform and more costly. It has also been suggested that unless research showed a decrease in complications with the transforaminal approach, it would be difficult to recommend this approach.[89] In summary, given that pain relief is transient, it is unlikely that the transforaminal approach would have improved the long-term outcome of the group.

As for ESIs, evaluation of this technique should be viewed within the context of multidisciplinary care.

Safety

An objective of this study was to evaluate the safety of epidural steroids. The incidence of any complications was no greater in the active group compared with placebo. One major complication (PDPH) occurred. However, there were no other adverse events attributable to ESIs in this study. ESIs are the procedure most commonly associated with malpractice claims in the USA, accounting for 40% of all serious complications in pain management.[37] The introduction of infection must be taken extremely seriously owing to the potentially dire consequences should meningitis or epidural abscess occur. The risk of such infections is quoted as less than 0.01%.[90] Permanent nerve damage is the most common neurological complication although, again, the incidence is very low.[91] This study did not find serious complications such as arachnoiditis or radiculopathy. Demonstrating the very low incidence of such serious adverse events is not achievable in a study of this size; thousands of patients would be required to shed further light. Perhaps the most effective way to do this would be through mandatory registration of all ESIs, as has been done for novel interventional procedures of unclear benefit. This has to be given serious consideration in view of the low efficacy of this procedure. Monitoring the competency of operators would be implicit in this. It may be concluded that ESIs are relatively safe, but the patient should be aware as part of the consenting process of the potential for serious, rare complications.

Cost-effectiveness

Engel and colleagues identified the patients responsible for high costs with low back pain as those with increasing chronic pain grade and those with sciatica.[92] Many of these costs are due to the fact that they have chronic disability. Costs of chronicity are both financial and psychosocial. These include extra medical attention, including radiographic investigation and surgery, long-term drugs, social benefits, loss of work, carer costs and family costs. Therefore, as these patients are costly, any effective intervention, however minor, would be worthwhile if they reduced the above costs. For some patients even a small difference in resolution of symptoms could be very worthwhile to the individual. This effect was clearly too small to translate into notable improvements in quality of life.

ESIs are often used in the management of sciatica and incur considerable costs to the healthcare system. Indeed, they are one of the most frequent procedures carried out in both public and private healthcare. From this study and figures from the National Health Service Information Authority (NHSIA), assuming a patient management strategy based on the trial protocol, purchasers spent £31,256,740 on ESIs in 2002 (*Table 13*). Although short-term benefits clearly were achieved in a minority of patients, this study demonstrates that there is no benefit of ESI in the medium or long term, in terms of pain relief, improvement in function, utilisation of further health services, including surgery, or return to work. Adopting a patient management strategy based on the trial results (one injection) to realise the transient benefit would be a saving of £16,505,700 to purchasers. Lafuma and colleagues presented similar results for a more intensive inpatient-based management strategy, although they did not report long-term outcome data.[45]

NICE has previously suggested a threshold of £30,000 per QALY. This figure has recently been challenged, and it is suggested that the threshold for treatment should be a cost per QALY of £18,000.[53] Under either benchmark, ESIs fail the QALY threshold from the perspective of both purchaser and provider. If no ESI were to be undertaken based on this guidance the total saving would be £31,256,740 from the purchaser's perspective.

Measured against implied NICE cost per QALY thresholds, ESIs should not be purchased under the NHS. However, the private benefits of transient relief by week 3 (compared with waiting until week 6) may be highly valued by the individual. These results therefore cannot be transposed into private clinical practice.

Chapter 8

Opinion and implications for healthcare

Cochrane asks three key questions when investigating a healthcare intervention:

- Can it work?
- Does it work in practice?
- Is it worth it?

It is well recognised that deciding that something does not work, especially a long-established procedure, is hard to do. Despite knowing that ESIs can and do work in practice, they may not be worth it.[93]

The present study did not find a place for ESIs in the early stages of the disease. This group believes that patient education in the early stages is of paramount importance. Important educational points are:

- Sciatica is likely to improve.
- The disc lesion will heal quickly.
- It is necessary to take analgesics.
- Full participation in an exercise programme is likely to help.

In secondary care sciatica appears to be a chronic remitting condition. The cohort of patients presenting to secondary care is highly disabled. It is unlikely that a single intervention such as an ESI will be effective in isolation. Given the severity of impact on psychophysical functioning these patients require a multidisciplinary assessment.

This study confirms the view that ESIs confer only short-term benefit. In addition, there were no predictors of response. They did not defer surgery. Short-term repeat injections made no difference. ESIs are relatively safe, but a large longitudinal study would better determine the true safety. The authors' opinion is that:

- The routine use of ESIs in sciatica needs to be urgently reviewed and its place re-evaluated.
- A National Registry of all ESIs may be a suitable method for collecting appropriate data on safety and predictors of response.

In this study, the estimated cost for an epidural, including assessment, procedure and follow-up, on the NHS in 2002 was £265.30 from the provider's perspective and £2102 from the purchaser's perspective, assuming a patient management strategy adopted in the clinical trial. Real resource savings to the provider would be £3,945,011 and £31,256,740 to purchasers if ESIs are no longer undertaken on the NHS, given that the cost per QALY ratio exceeds the NICE threshold.

The resource savings are substantial even if there is a modest change to treatment. For example, from the purchaser's perspective, the saving of moving from an assumed model of current pragmatic management practice (a maximum of three ESIs) to a patient management strategy suggested by the trial results (one ESI) would represent a saving of £16,505,700 in the sector. The costs of ESIs to purchasers as used in their present form do not, in the authors' opinion, represent good value for money and indeed fail the QALY threshold.

Chapter 9

Areas for future research

Further research is suggested in the following areas.

- Additional work on the epidemiology of radicular pain is needed so that patients can be presented with better information on prognosis.
- A register of all ESIs should be developed so that the true incidence of major complications can be accurately determined.
- Subgroups that may benefit from ESIs may be identified through very large trials. These need not have long-term follow-up, but a wider range of assessment tools may be necessary to detect small changes in function. A subgroup analysis of acute and chronic patients may be one of these groups.
- Although previous studies have been inconclusive, the use of radiological imaging may improve accuracy and should be investigated further in larger studies with respect to outcome.
- Additional work on the optimal early interventions may reduce the incidence of severe persistent sciatica. This is likely to require a multidisciplinary approach even at an early stage with involvement of vocational rehabilitation.
- A systematic review of analgesic agents and nerve root injections would determine the research agenda for these two potential analgesic strategies.
- Other more novel methods to reduce the effect of scarring and inflammation should be explored.
- The use of CBT in rehabilitation should be explored further.
- Exploration of improved methods of assessment to include investigation of cognitive content and processing in those with sciatica may better determine specific rehabilitative strategies.
- A comparative cost–utility analysis between various treatment strategies for sciatica would help purchasers in decision-making.

Chapter 10

Conclusions

In conclusion, ESIs offer no sustained benefits to patients with sciatica in terms of pain, function or need for surgery. It may be concluded that lumbar ESIs have a weak, transient effect that is insufficient to provide a meaningful difference to patients in terms of functional improvement. If improved physical function can be equated with improved health and reduced burden of healthcare, then lumbar ESIs produce no enduring improvement. Indeed, this was borne out by all other indices of health that were used in the study.

Cases of sciatica that present to secondary care produce major long-term morbidity. These patients have severe disability and distress with a major impact on social functioning. The vast majority of these cases fail to respond to current conservative measures. This is borne out by the high number of protocol withdrawals owing to lack of efficacy at 12 weeks. This should not be seen as a recommendation to increase back surgery, which carries substantial risk in terms of treatment failure and morbidity.

Although this study did not directly compare one ESI against three ESIs, no evidence was found for repeat injections in the short term or for their use early on in the care pathway. ESIs should not be used as a means of deferring surgery. They offer transient benefit in a minority of patients, but this has to be balanced against the significant costs incurred by these procedures. More accurate methods of placement may enhance the effect, but this may incur further costs. However, all the effects of these injections are transient. The optimal analgesic strategy has yet to be determined. Increased use of neuropathic pain analgesics and supervision of other drugs may enhance compliance.

ESIs should be seen as part of a package of rehabilitative care where a coherent analgesic strategy is provided and potential psychosocial barriers to rehabilitation are addressed in a systematic fashion. It can be seen that the decision to offer an ESI as treatment is complex. The patient needs to be involved in this process. Patients should be aware that some degree of pain is likely to be long lasting and enduring. Coulter defines the concept of patient-centred care as "informing and involving patients, responding quickly and effectively to patients' needs and wishes, and ensuring that patients are treated in a dignified and supportive manner".[95] The implication here is that physicians who perform ESIs for sciatica should only be those who are prepared to take time assessing patients carefully and discuss their treatment options with them, and who have ready access to full pain management rehabilitation strategies. Improvement in healthcare is dependent on having good information on which to make decisions. Much information is missing on sciatica. What is the epidemiology of sciatica? How can sciatica and its sequelae be prevented? Why are some cases chronic and how can prevention of chronicity be achieved? Why do some people return to work and others become invalids? These are questions beyond the scope of the study that require answers if sciatica is to have less of an impact on sufferers' lives than it currently does.

Acknowledgements

WEST Study Group
John Stubbing, Elizabeth Arden, Nicola Chaderton, Jane Hazelgrove, Angela Bell, Ciaran Dunne, Sally Sawyer, Maher Michel and Paul Thompson.

We thank Portsmouth, Poole, Bournemouth and Southampton pain and rheumatology staff for their patience, Isabel Reading (Statistician, MRC Environmental Epidemiology Group) for statistical analysis of the study, Jane Hazelgrove for review and assistance with preparing the manuscript, Cathy Benyon (Finance Department, Southampton University Hospitals Trust) for financial information, Professor Cyrus Cooper for review of the manuscript, and all the referees for their constructive comments.

Contribution of authors

Cathy Price (Consultant in Pain Management), Louisa Coglan (Assistant Professor) and Nigel Arden (Senior Lecturer) wrote the protocol. Nigel Arden managed the trial and data analysis. Cathy Price, Louisa Coglan and Nigel Arden wrote the final document. Peter Rogers (Consultant in Pain Management) managed the financial aspects of the trial and contributed to the protocol and final document.

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Appendix 1

Protocol

Background to the project: definition and epidemiology

Sciatica is a common complaint that is defined as unilateral, well-localised leg pain that approximates to the dermatomal distribution of the sciatic nerve and normally radiates to the foot or toes. It is often associated with numbness or paraesthesia in the same distribution.[1] In the majority of cases the natural history of the disease is of spontaneous resolution; however, some studies have reported that 30% had significant symptoms at 1 year, with 20% out of work and 5–15% requiring surgery.[2,3] Little work has been done on the epidemiology of sciatica in the UK, but a Finnish study reported the lifetime prevalence of sciatica to be 5.3% in men and 3.7% in women with sciatica, representing 6% of the total work disability of the population.[4] The cost of conservatively treated sciatica was estimated at £30,000 in a recent US study.[5]

Sciatica was initially thought to occur predominantly as a result of prolapsed lumbar vertebral disc causing compression of the nerve root, leading to neural ischaemia, oedema and eventually to chronic inflammation, scarring and perineural fibrosis. It is now evident that sciatica can occur in the absence of direct nerve root compression, probably as a result of the release of phospholipase A_2 and other proinflammatory agents from a damaged disc leading to nerve root inflammation and oedema.[6] Pain occurs because of chronic, repetitive firing of the inflamed nerve roots.

Rationale for the use of epidural corticosteroids

Therapeutic alternatives include: conservative therapy (rest, physiotherapy, and analgesia), epidural steroid injection (ESI) and surgical decompression. None of these strategies has complete success, but ESIs have been regarded as a useful addition to therapy. The majority of epidural injections performed for sciatica use a local anaesthetic agent and a long-acting corticosteroid. It is thought that the majority of the therapeutic benefit achieved by epidural injections is due to the anti-inflammatory effects of corticosteroids in reducing perineural inflammation. However, local anaesthetic agents alone may have some effect by reducing painful muscle spasm, interrupting repetitive radicular firing and interfering with any sympathetic elements. It is not clear what proportion of benefit is due to the corticosteroid and to the local anaesthetic agent, but the combination of a corticosteroid and local anaesthetic agent has been shown to be more effective than local anaesthetic alone.[7]

Previous studies of epidural corticosteroids

Initial uncontrolled studies with epidural steroids gave promising results;[8] however, the results of clinical trials have proved inconclusive. Many clinical trials have been performed, but only nine have studied sciatica in isolation and have been randomised and blinded. Of these, four found significant improvement with epidural steroids[9–12] and five found little objective benefit.[13–17] There are several methodological differences between these published studies that make it difficult to draw any firm conclusion from them.

- Statistical power: the majority of the studies have had limited statistical power to detect anything less than major treatment effect sizes, with only two of the studies containing 50 or more patients in each arm.[12,16]
- Placebo: the placebo used in each study has varied from intraligamental saline[10,12] to epidural anaesthetic in equal volumes to the active arm,[14,17] making comparisons between studies difficult.
- Study population: the populations studied have varied between studies from radiologically proven disc lesions[13,14,16] to sciatica diagnosed clinically with no imaging.[10–12,15,17] Individual studies have often recruited heterogeneous populations (including the chronicity of symptoms) but no attempt was made to identify any subgroups that may have responded.
- Route of injection: both the caudal[9,11] and lumbar[10,12–17] approaches have been used in previous studies. There is some suggestion that the lumbar approach may be a more accurate approach to reach the epidural space and often places the steroid closer to the inflamed root.

- Follow-up: many studies have used only extremely short-term follow-up at 24–48 hours as their primary outcome measure;[13,14] furthermore, the timing of the assessment of the primary outcome measure has varied markedly between studies.
- Outcome measures have varied between studies.[9–11,13–15]

Several of these studies suggested that epidural steroids offer only short-term benefit,[7,9,10,12,16] with little benefit on long-term follow-up,[11,13,14] the conclusion reached by a recent meta-analysis.[18] However, this did not address several of the flaws mentioned above, and its validity is questionable owing to the heterogeneity of the studies incorporated in it.[19] A systematic review included many of the above criticisms, but failed to distinguish between low back pain and sciatica, which may have differing aetiologies.[20] In patients obtaining partial relief of symptoms, further benefit has been obtained by repeated epidurals, up to a total of three.[21,22]

The most recent study[16] was of good design and larger numbers and had objective outcome measures measuring disability. This failed to show any significant improvement in function, although there was some small improvement in pain with epidural steroids at 3 months. The majority of patients in this study had had sciatica for only a short period and had significant disc prolapse on computed tomographic (CT) scan. They may not have been expected to do well conservatively. This profile does not fit the majority of UK patients.

No study has directly identified a subgroup of patients who respond better to corticosteroids, although it is postulated that those with perineural oedema without direct neural compression would respond well. There is evidence to support this hypothesis, as all three studies including patients with radiologically proven disc lesions have reported no benefit from epidural injection.[13,14,16] Jamison looked at predictors of poor short-term outcome from epidural steroid injection for low back pain and sciatica.[23] It appears that a large number of treatments, and pain worsened by activity and coughing, may be factors. Beliveau suggested that those with chronic disease (over 6 months) may do better.[17]

Thus, it appears that steroids may benefit those who have less severe disc prolapse, that the benefit may be short to medium term only, and that the effect may be relatively small. Chronicity of the symptoms may be a factor in determining response to injection. These issues have been borne in mind when designing this study.

The place of MRI in degenerative disc disease has not been fully established. MRI-demonstrated lesions correspond well with operative findings; however, the majority of disc bulges and protrusions are asymptomatic.[24] Although MRI findings correlate well with clinical findings for site and level of a disc herniation, they correlate poorly with the severity of symptoms.[25] This is thought to be due to the fact that pain is more due to inflammation than to compression. The role of MRI in predicting the long-term outcome of sciatica is not fully understood.[4,26] The authors are unaware of any study comparing MRI results with the response to ESI.

Epidural steroids have also been the subject of debate on the grounds of safety. A review of this issue concluded that the majority of complications with steroids occur as a result of intrathecal injection and not epidural injection.[27] Although intrathecal injection may occur with epidural injection it was considered unlikely. The complications that have been reported are epidural abscess, meningitis, hypercorticism and allergy.[28] These are so rare that they are the subject of isolated case reports. Arachnoiditis, associated with intrathecal steroids, has not been linked with epidural steroids, although theoretically this is a risk. The main concern has been the use of preservatives in the steroid formulation. Triamcinolone contains the least amount of preservative of the available steroids and its use is endorsed by the British Rheumatological Society and Pain Society, hence the choice of triamcinolone as steroid in this study.

With regard to cost-effectiveness, little work has specifically looked at sciatica. One retrospective study compared prolonged conservative treatment with surgical treatment and found no difference in outcome and therefore no difference in cost-effectiveness.[5]

Outcome measures for sciatica have been evaluated previously.[29] Assessment of outcome is complex and needs to be multidimensional. Five measures are thought to be important:

- pain assessment
- clinical assessment
- medications
- levels of disability
- psychological assessment.

There is increasing clinical consensus that functional measures of disability have greater reliability and relevance than measures of pain.[1] Work loss is the most objective measure, but is limited in terms of applicability (e.g. young and old are excluded) and other socioeconomic factors. Therefore, level of disability was chosen as the main outcome measure. The Oswestry index[30] has been widely used in back pain research and was the main outcome measure chosen in the most recent trial of epidural steroids in the treatment of sciatica. A score of less than 20% represents minimal disability. Therefore, the Oswestry index was chosen as the main outcome measure.

Special circumstances as to why this group is ideally placed to run this trial

The study proposed is multicentre and multidisciplinary in design. The MRC Rheumatology Unit and its members, Nigel Arden and Cyrus Cooper have been involved in several HTA projects. Computing, statistical and epidemiological expertise are also readily available. Peter Rogers has previously published in this area.[7] At each centre patients will be assessed for eligibility by experienced rheumatologists and the injections performed by experienced anaesthetists.

The centres proposed are all within the boundaries of one health region and good relationships between each of the departments are already well established. At Poole and Bournemouth hospitals there is a fast track service available for sciatica and therefore these will provide the majority of acute patients, whereas Southampton and Portsmouth will provide mainly patients who have had sciatica for longer than 4 months. Pilot studies also indicate that between the four centres enough patients are seen per annum to recruit comfortably the required numbers in 12 months, even allowing for up to 60% of patients declining to participate in the study.

Plan of investigation

Research objectives

- To examine the efficacy and cost-effectiveness of lumbar epidural injections in the management of sciatica.
- To examine the efficacy and cost-effectiveness of baseline MRI scans of the lumbosacral spine in predicting outcome of epidural injections and the need for surgery.

Design

A pragmatic, multicentre, 52-week, randomised, double-blind, placebo-controlled study.

Subjects

All patients aged between 18 and 70 years presenting with sciatica will be considered for the study, subject to the following inclusion and exclusion criteria. This mirrors the current clinical practice for the use of epidurals in the management of sciatica in this region.

Inclusion criteria:

- back pain with unilateral radicular symptoms, extending below the knee, and signs including reduced SLR and a positive sciatic nerve stretch test
- duration of symptoms for a minimum of 4 weeks and a maximum of 18 months
- normal full blood count, erythrocyte sedimentation rate and basic bone biochemistry
- lumbar spine X-ray to exclude other causes of radicular pain including infection or malignancy.

Exclusion criteria:

- previous back surgery
- bleeding diathesis or use of anticoagulants
- bilateral symptoms
- previous epidural injection
- current litigation relating to the sciatic symptoms or significant psychological disorders.

Recruitment

Patients will be recruited from the rheumatology clinics and pain clinics in the four participating centres: Southampton, Portsmouth, Poole and Bournemouth hospitals. Poole and Bournemouth hospitals already operate a fast track epidural service, seeing patients within 2 weeks of referral. Similar arrangements will be made at Southampton and Portsmouth hospitals.

Pilot study

The four centres currently perform a total of 1100 epidurals on new patients for sciatica per year. The numbers for each centre are as follows:

Portsmouth	230
Southampton	220
Poole	400
Bournemouth	250

Of the patients receiving epidural injections for sciatica, 75% fit the criteria for entry into the study, leaving a total of 825 patients per year fitting the study entry criteria. Approximately 45% of patients attending these clinics at present have acute (less than 4 months' duration) sciatica.

The results of the pilot study suggest that 40% of subjects fitting the entry criteria would be willing to participate in the study. This gives a potential recruitment rate of 300 patients per year.

Randomisation

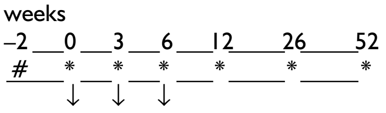
Subjects will be randomised to treatment or placebo group using random permuted blocks of ten. The randomisation will be performed separately for each centre and will be stratified for the duration of disease (less than or more than 4 months).

Interventions

- Treatment group: lumbar epidural injection, using standard techniques, of 80 mg triamcinolone acetonide and 10 ml 0.25% marcaine
- Placebo: injection of 2 ml of normal saline into the interspinous ligament with identical preparations and needles to the treatment group.

All patients will receive a standardised physiotherapy package at the beginning of the study, focusing mainly on education and exercise regimens. They will be allowed to consume analgesics and anti-inflammatory medicines as required. This mirrors current practice in the region.

Study details: visits



#, Assessment by rheumatologist to assess eligibility; *, assessment by study nurse; ↓, injections.

The patients will be assessed initially by a rheumatologist to assess the eligibility of each patient to enter the study and to obtain the patient's informed consent.

Each patient will be assessed at 0, 3, 6, 12, 26, and 52 weeks by a trained research nurse, who will be blind to the patient's treatment status. There will be three research nurses working on the project. All will receive standard training in the relevant research tools to be used, and both interobserver and intraobserver reliability will be tested until acceptable standards have been achieved before commencing the study.

At each visit the following will be performed:

- Oswestry low back pain disability questionnaire
- Short Form 36 (SF-36)
- visual analogue scale for both back and radicular pain
- McGill pain questionnaire
- analgesic intake
- work status
- objective measures of sciatic root irritation: straight leg raising and neurological deficit
- Beck Depression Index questionnaire (first visit only)
- side-effects of the procedure.

At the end of the study patients will be asked which treatment arm they thought they were in, to assess the efficacy of blinding.

Repeat injections

Injections, according to study group, will be repeated at 3 and 6 weeks according to response. The indication for a repeat injection is less than a 75% improvement in Oswestry disability score from the baseline visit. Patients and the research nurse will continue to be blind to the injection performed.

Code breaking

The patient's code will be broken if either or both of the following criteria are fulfilled:

- any deterioration in neurological symptoms
- less than a 10% improvement in Oswestry disability index at 12 weeks or subsequent visits.

Outcome measures

Primary:

- Oswestry low back pain disability questionnaire

Secondary:

- pain: VAS, McGill
- return to work
- analgesic intake
- surgery
- neurological signs (straight leg raising, sensory deficits, reflex changes).

Power calculation

The Oswestry low back pain disability questionnaire will be used as the primary outcome. Its standard deviation in a population of subjects with sciatica is 15.6 points.[16] Using $\alpha = 0.05$, $\beta = 0.1$ and 120 patients in each arm, and allowing for a 20% dropout rate a treatment difference of 7.25 points could be detected. This will give ample statistical power to detect any meaningful clinically relevant treatment effect, thereby minimising the chance of inconclusive results.

An alternative method of calculating statistical power is to use the dichotomous outcome measure based on the Oswestry questionnaire. A successful outcome will be defined as a 75% improvement in the Oswestry questionnaire score.

Assuming that 50% of the placebo arm have a successful outcome,[16] using $\alpha = 0.05$, $\beta = 0.1$ and allowing for a dropout rate of 20%, a success rate of 72% in the treatment arm could be detected.

Statistics

Efficacy analysis

An intention-to-treat analysis will be performed using the Oswestry low back pain questionnaire as the main outcome variable. All dropouts will be recontacted by mail and telephone approaching their 52-week visit to obtain updated information. Mean improvement in each group will be compared by an unpaired *t*-test and by analysis of variance to adjust for any poorly matched baseline characteristics. Subset analyses will be performed to assess the efficacy of epidural injections in patients with acute and chronic sciatica.

Analysis of secondary outcome measures will be analysed similarly for continuous variables and by the χ^2 test for dichotomous variables. Analysis of surgical intervention and return to work will be performed using Kaplan–Meier survival analysis and the log-rank test.

Cost-effectiveness analysis

Study question

From the viewpoint of hospital purchasers, are steroid epidural injections in the management of sciatica preferable to the alternatives? The alternatives considered will be:

- physiotherapy, education and analgesia
- steroid epidural injection, physiotherapy, education and analgesia
- MRI scan, steroid epidural injection, physiotherapy, education and analgesia (optional).

These alternatives cover clinical practice. It was felt not to be appropriate to include a 'do nothing' option for the cost-effectiveness study. The viewpoint of the study will ensure that the results are of use in decision-making scenarios for those who manage and work in the NHS.

The primary analysis will be a cost–utility analysis using the Oswestry low back pain questionnaire[30] as the main outcome measure. To ensure that no multidimensional aspects of outcomes are missed, a generic outcome measure, the SF-36, will also be used.[31]

A cost-effectiveness analysis will also be performed using two separate outcomes:

- Return to work would be the most appropriate outcome measure, but there are inherent difficulties of its definition and collection in a population of mixed age, gender and socioeconomic groups.
- Operations averted is a hard clinical outcome measure which is easy to define, cost and collect.

The previous studies of epidurals have been heterogeneous in design and outcome measure and have often not presented outcome measures of use for cost-effectiveness analysis. This study has sufficient power to answer the questions and therefore previous studies will not be incorporated into the analysis.

Costs

Given the study perspective, only direct costs will be explicitly considered. Costs will be based on the standard resource cost assumptions from the decision-makers' perspective.[31,32] Direct costs will be collected during the RCT for the different clinical settings. Costs will be generalised to represent those of the general practice. Differences in costs of the clinical settings caused through variation in practice (i.e. variations in skill mix) will be made explicit and presented in the results.[33]

Direct costs will include:

- overhead costs: these will be estimated by the allocation method. The method used will depend on the importance of this item, such as simple per diem costs to direct allocation if they are found to be significant
- labour costs
- medical equipment costs.

Actual resource use will be determined by a survey of clinicians involved and by observation of practice. It is expected that the latter will yield the more reliable estimates.

Although it is recognised that significant indirect costs savings would be generated by successful pain relief by enabling patients to return to work, these will not be considered. Collection of such costs would be based on a number of assumptions, specifically that the patient population would return to employment. Thus, there is a danger that inclusion of indirect costs would significantly overstate potential cost savings. In addition to this it is argued that indirect cost savings are irrelevant in resource allocation decisions.[31]

All participating centres have agreed to release costs.

Differential timing

An adjustment for differential timing will be made at the standard government discount rate.

Sensitivity analysis

Sensitivity analysis will be comprehensively conducted for all key parameters. The results of the sensitivity analysis will be presented in standard form (i.e. switching values and sensitivity indicators).

Results

Outcome measures will be combined with costs and the respective ratios presented in a user-friendly format to allow managers and clinicians to make appropriate resource decisions.

Magnetic resonance imaging

As an optional extra, all patients will undergo an MRI scan of the lumbosacral spine, between the initial screening visit with the rheumatologist and the epidural injection. Patients, research nurses and all doctors will be blinded to the results until the end of the study. The standard lumbar spine protocol will be used. Patients will be placed on the spinal coil and scanned from the thoracolumbar junction to the mid-sacrum. Sagittal T1-weighted images will be obtained using a coronal localiser, followed by sagittal T2 images using a fast spin echo. Nine sagittal images with 5 mm width and 1 mm interspacing will be acquired, covering both exit foramina and facet joints. In-line axial sections will be performed for the lower three discs, with T1 weighting angled at disc orientation.

All scans will be read by two independent consultant radiologists, who are blinded to patients' details and randomisation, using validated techniques. Scans will be read with each patient's spinal radiographs to define abnormal segmentation and allow numbering. Aspects of the scan that would be evaluated include lumbar lordosis, marrow signal, vertebral body abnormality, vertebral alignment, disc hydration, disc morphology, disc protusion (lateral or posterior), disc herniation alone and with associated neural deviation or compression, and sequestered discs.[25,34]

This would enable three additional research questions to be addressed:

- Does an MRI scan predict response to an epidural injection of steroid?
- Is it cost-effective to perform an MRI scan, either complete or limited (e.g. T2 sagittal only) on all patients currently receiving epidural injections for sciatica?
- In the placebo group, does MRI scanning predict the outcome of sciatica?

Project milestones

- August 1998: recruitment and training of nursing staff
- November 1998: patient recruitment begins
- February 2000: patient recruitment completed, data entry begins
- February 2001: study completed, analysis begins
- May 2001: completion of study and report submission.

Methods for disseminating and implementing research results

The particular dissemination processes which will be pursued are:

- All applicants will take the opportunity to present their findings to their peer groups.
- There will be presentations at, in particular, the British Society of Rheumatology annual general meeting and the International Association for the Study of Pain biennial meeting.
- Findings will be posted on the Internet at a site within the Pain Society and/or British Rheumatological Society website.
- Other interested parties outside the participating specialities (e.g. GPs and orthopaedic surgeons) present more of a challenge. Dissemination via regional health authority's, acute Trust and GP circulars in the form of mailshots would appear the most effective methods.

Justification of the support requested

- Three part-time research nurses are required for 30 months to interview and examine the patients at all visits. This includes 3 months for training and setting up, 15 months for recruitment and 12 months of study follow-up. F-grade salaries are required to recruit nurses of a suitable calibre to work independently, perform administrative tasks and solve problems.
- In a field with many studies of limited statistical power and conflicting results, it is essential to perform a highly powered study to prevent the need for replication of similar studies. This degree of statistical power will also allow subgroup analysis to be performed with the power to detect most clinically significant differences.
- It is important to follow patients at regular intervals for 12 months to examine short-, medium- and long-term benefits of ESIs.
- It is important for all patients' care and compliance that they receive standardised physiotherapy at an early stage of the study. Waiting times for NHS referrals run at over 3 months locally and therefore physiotherapy time will need to be bought in.
- It is essential to purchase time from a health economist to perform the cost-effectiveness analysis.
- Data entry will be performed by research assistants who are trained in data entry and checking.
- MRI scans give the best anatomical definition of the lumbosacral spine, but are expensive and time consuming. Their use in clinical sciatica varies between specialities and regions, and the definition of their cost-effectiveness would provide useful information in standardising their use across the UK.

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Appendix 2

Derivation of epidural costs

Resource-use data

Resource-use data were collected across all three centres during the period July 2000 to October 2000. Results of the survey are presented in *Tables 16–22*.

Size of samples from each of the centres in the study are presented in *Table 16*.

In total, 151 record sheets were completed. Centre 2 recorded the largest return.

Nurse and clinician resource use across all three trial centres

Mean resource use and standard deviations relating to nurse and clinical time spent on a patient presenting to the clinic with sciatica for referral, procedure and follow-up are reported in *Tables 17–22*.

There was considerable variation in average values between the centres. This probably reflects differences in practices and cultures between the three centres, rather than any marked differences

***TABLE 16** Survey size from the three trial centres (total patient numbers)*

	Centre 1	Centre 2	Centre 3
Pre-epidural consultation	9	14	7
Epidural consultation	4	77	12
Review	3	22	3

***TABLE 17** Nurse time involved in patient referral (minutes)*

	Centre 1	Centre 2	Centre 3	Total
Setting up clinic	5.6 (1.7)	9.1 (5.6)	9.3 (5.3)	8.1 (4.9)
Consultation	15.6 (9.5)	28.6 (12.6)	38.6 (12.1)	27.0 (14.2)
Additional time with patient	4.4 (1.7)	7.5 (15.2)	5.6 (2.0)	6.1 (10.3)
Patient administration	5.6 (1.7)	5.1 (1.2)	4.1 (1.9)	5.0 (1.6)
Assisting patient	6.7 (3.5)	2.7 (3.0)	5.1 (2.4)	4.5 (3.5)
Total	37.8 (12.5)	53.0 (14.7)	62.7 (12.0)	50.7 (16.1)

***TABLE 18** Clinician time involved in patient referral (minutes)*

	Centre 1	Centre 2	Centre 3	Total
Consultation	18.9 (9.9)	32.0 (10.0)	37.9 (9.9)	29.5 (12.1)
Patient administration	8.9 (2.2)	9.7 (3.3)	7.9 (2.7)	9.0 (2.9)
Total	27.8 (9.7)	41.7 (12.7)	45.7 (12.4)	38.5 (13.5)

***TABLE 19** Nurse time involved in epidural procedure (minutes)*

	Centre 1	Centre 2	Centre 3	Total
Admitting patient	17.5 (6.5)	13.2 (13.0)	10.6 (8.0)	13.0 (12.3)
Assisting patient during procedure	18.8 (2.5)	20.3 (11.6)	16.3 (7.4)	19.7 (11.0)
Assisting clinician during procedure	23.8 (7.5)	13.6 (11.7)	14.9 (8.1)	14.2 (11.2)
Time spent one-on-one with patient in recovery	42.5 (28.7)	16.1 (14.7)	29.1 (23.6)	18.9 (17.8)
Other patient administration	15.0 (4.1)	7.9 (9.4)	11.7 (7.2)	8.7 (9.1)
Total	117.5 (39.3)	71.1 (29.4)	82.5 (38.3)	74.6 (32.2)

TABLE 20 Clinician time involved in epidural procedure (minutes)

	Centre 1	Centre 2	Centre 3	Total
Consultation	7.3 (2.1)	25.9 (14.9)	20.4 (7.8)	24.4 (14.4)
Patient administration	6.3 (4.8)	6.1 (3.0)	7.8 (3.3)	6.4 (3.2)
Total	13.5 (6.6)	32.0 (16.0)	28.3 (8.7)	30.8 (15.4)

TABLE 21 Nurse time involved in review (minutes)

	Centre 1	Centre 2	Centre 3	Total
Setting up review visit	5.0 (0.0)	5.8 (4.8)	2.5 (3.5)	5.4 (4.4)
Assisting patient	5.0 (0.0)	1.3 (1.1)	7.5 (3.5)	2.2 (2.3)
Assisting patient/clinician during the consultation	13.3 (2.9)	11.9 (7.2)	12.5 (3.5)	12.1 (6.6)
One-on-one with patient	6.7 (2.9)	1.8 (1.9)	7.5 (3.5)	2.8 (3.0)
Other patient administration	5.0 (0.0)	3.4 (2.1)	3.5 (2.1)	3.6 (2.0)
Total	35.0 (5.0)	24.2 (11.3)	33.5 (2.1)	26.2 (11.0)

TABLE 22 Clinician time involved in review (minutes)

	Centre 1	Centre 2	Centre 3	Total
Consultation	20.0 (0.0)	12.6 (6.6)	7.5 (10.6)	13.0 (6.9)
Patient administration	15.0 (13.2)	4.6 (2.4)	6.0 (5.7)	5.9 (5.5)
Total	35.0 (13.2)	17.2 (7.6)	13.5 (16.3)	18.9 (10.2)

in quality of patient care. For example, in the case of the epidural procedure, the time spent by nurses in centre 1 was almost double that in centre 3, but centre 3 had almost double the clinician time.

Unit cost data

NHS recharge costs were obtained at the local level (Southampton) and national level (average). However, these costs are only indicative of accounting charges against cost centres and are not representative of economic costs. Unit cost data were therefore determined for the key inputs into the management and treatment of patients who received epidural injections for the treatment of their sciatica. This included labour costs, associated medical costs of the procedure, other costs (e.g. pathology and radiography) and overhead costs.

All costs are expressed in 2002/03 prices.

Labour costs

As the major input into the treatment was labour, the actual resource cost is related to the salary of the staff providing the treatment. As salaries vary based on experience, it was considered appropriate to apply a common labour charge across all three centres. Labour costs for centre 3 were used for this purpose. Labour costs were inclusive of National Insurance and superannuation costs (i.e. the full cost of employment).

Clinician labour cost per hour is based on a consultant's hourly wage. This biases the costs of this input to the upper cost end of the salary scale. An alternative would have been to calculate an average clinician cost per hour based on all grades of clinician able to conduct an epidural consultation (e.g. from specialist registrar to consultant with discretionary points). However, this cost would have been biased by the low cost of specialist registrars [approximately 50% less than consultants' hourly rate (*Table 23*)] who are not atypical of the clinicians who act in this consultation capacity.

TABLE 23 Clinician costs per hour (£, 2002/03)

Grade	Hourly cost
Consultant with discretionary points	46.35
Consultant	33.83
Specialist registrar	17.35

TABLE 24 *Nurse costs per hour (£, 2002/03)*

Nursing grade	Hourly cost
G	14.96
F	12.86
E	11.31
Average nurse costs per hour	13.04

TABLE 25 *Breakdown of costs of epidural injection (£, 2002/03)*

Sundries	Cost per amount used
Packs and dressings	
Basic spinal dressing pack	6.38
Mini epidural pack	7.50
Gloves, one pair	0.54
Cannula	1.15
Non-sterile gloves, one pair	0.04
Patient ID bracelet	0.07
Microtape	0.07
Sterile gown (including laundry costs)	2.50
Medicines used in an epidural	
Triamcinalone 80 mg	1.77
Marcaine 0.25% 10 ml	1.26
Lignocaine 1% (10-ml ampoule)	0.53
Hydrex[a]	0.06
Total	21.87

[a] Based on an approximate amount. Some doctors also use other skin preparations; Hydrex is the cheapest.

Nurse costs were calculated as an average of three staff grades (E, F and G) assuming that no shift payments were made (*Table 24*).

Medical costs of procedure (epidural injection)

The medical costs of procedures (the epidural injection) were calculated as £21.87. This was derived from a bottom–up detailed costings approach (*Table 25*).

Other costs

Costs associated with a standardised physiotherapy package (focusing mainly on education and exercise regimens) were not considered as these patient costs would be incurred regardless of whether a patient presenting with sciatica received an epidural or not.

Although there was an apparent difference in analgesic use between the two groups (*Table 24*), this was not statistically significant. This indicates that there was a large variation in use in both groups. The apparent difference occurred even before the trial (i.e. week 0). Normalising the analgesic use to look at changes in use results in similar patterns between the two groups (*Figure 10*). As a result, differences in analgesic use were not considered a consequence of the treatments, just an artefact of the sample. Analgesic costs therefore were assumed not to differ between the two groups and were not considered in the economic analysis.

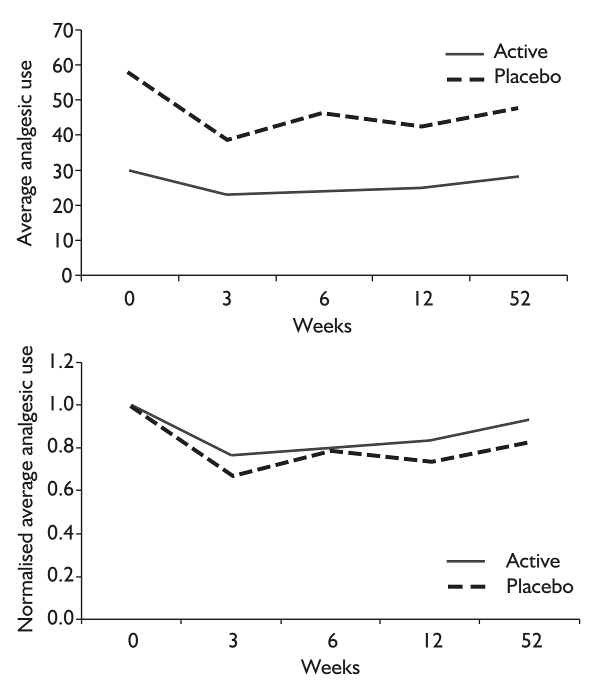

FIGURE 10 *Average and normalised analgesic use*

Costs associated with radiology and pathology were incurred after the initial review if not already performed by the referring source. These costs were reported as £18 and £2.10, respectively, from the finance directorate. Health service utilisation after week 52, specifically surgery, other injections and further physiotherapy, was recorded but no significant difference was found between the two groups (*Table 24*). Consequently, the costs of these were not included in the economic analysis.

Other costs incurred by patients, such as an overnight stay (£75), were included in the sensitivity analysis.

Overhead costs

Overhead costs were calculated based on adding 20% to direct costs. This was as advised by the financial directorate of one Trust. Administration other than that undertaken by nurses and clinicians was assumed to be negligible, so their costs were not included. Effectively, it was assumed that there would be no administrative resource savings from the perspective of the Trust by not treating these patients. (The hourly cost of administration and clerical support ranged between £6.88 and £8.38. If it is assumed that each patient needed 5 minutes of administration this adds between 55 and 67 pence per patient to the average patient cost.)

◆

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ISSN 1366-5278