Background

Prevalence and cost of low back pain

During each year 36 to 48% of UK adults recall having low back pain[1] [2] [3]. Lifetime prevalence has been estimated to be in the range of 58% to 62%[4] [2] [3]. In the UK the economic burden of back pain in terms of healthcare costs and lost productivity is around £12 billion[5]. In most acute cases seen in primary care, the pain is limited to the lower back and will resolve after a few days to a few weeks. However, some cases develop chronic pain and disability[6] and have referred symptoms of pain, sensory disturbance (e.g. numbness) and weakness extending to the buttocks, thigh or foot. In a minority of patients with low back pain, a diagnosis of lumbar radiculopathy is made when lower limb symptoms are thought to originate from inflammation or compression of the dorsal nerve root or ganglion.

Frequency of lumbar decompressive surgery and patient outcomes

Substantial numbers of patients with persistent low back pain are treated surgically. In 2008/9 there were more than 10,000 primary excisions of a lumbar intervertebral disc performed on NHS inpatients in England. Randomised trial evidence on the effectiveness and cost-effectiveness of lumbar discectomy in patients with radiculopathy and intervertebral disc herniation is not definitive. The SPORT trial randomised 501 patients to open discectomy or non-operative care[7]. Pain, physical function and disability improved substantially in both groups by 2 years, between group differences favoured surgery but were non-significant. Interpretation of the trial is hampered by substantial non-compliance (only 50% randomised to surgery received it) with treatment allocation. In 2008/9 there was one revision lumbar discectomy for every nine primary lumbar discectomies performed on NHS patients. Improved diagnosis could help identify patients most likely to benefit from surgery and minimise the cost and risks associated with unsuccessful back surgery.

Diagnosis of the cause of low back pain and the role of selective nerve root blocks

The exact cause of low back pain is often difficult to diagnose. In most patients, the diagnosis of radiculopathy is made by careful correlation of clinical signs and symptoms (e.g. pain distribution, paresis, straight leg raising test) and imaging findings (e.g. evidence of disc herniation and nerve root compression on MRI or CT myelography). But neither clinical findings[8] nor anatomical imaging have perfect diagnostic accuracy. Patients often find it difficult to precisely define the boundaries of their leg pain, sensory disturbance or weakness. MRI studies on volunteers have demonstrated surprisingly high rates of asymptomatic disc protrusions, extrusions, with associated nerve root compression[9]. Therefore clinical and imaging evidence of nerve root compression are frequently not completely concordant. In these cases, additional diagnostic tests such as selective nerve root blocks (SNRBs) could help clinicians and patients to choose between surgical and conservative care.

Selective nerve root blocks

SNRBs have been employed since the 1930s as a method of confirming the source of radicular pain prior to surgery [10]. Diagnostic SNRB consists of injection of local anaesthetic around spinal nerves under imaging guidance. Both provocative responses (replicating the patient's symptoms during needle placement) and analgesic responses (significant reduction of symptoms after injection) to SNRB may be diagnostically useful in confirming or ruling out a nerve root as the source of clinical symptoms. Recent international consensus statements have concluded that properly performed diagnostic SNRBs '…are useful when the location of symptoms seems to conflict with abnormalities identified with imaging findings…'[11], although the evidence on this topic was categorised as being of only moderate quality. The diagnostic value of SNRB should be weighed against the small risk of complications associated with

the procedure. A study of 1,777 procedures observed 98 (5.5%) transient post-procedure complications such as leg weakness or light-headedness[12]. More rarely, there are case reports of more serious complications, such as paraplegia[13].

The therapeutic impact and cost-effectiveness of selective nerve root blocks

The impact of 'diagnostic' SNRB results on treatment decisions is not well studied. Although not primarily designed to evaluate the therapeutic impact of diagnostic SNRB, data reported by Sasso et al suggest that only 8% of patients with a negative SNRB test subsequently had surgery at that lumbar level compared to 21% of patients with a positive SNRB ($p<0.01$)[14]. These observational data are indicative, but cannot determine whether the SNRB result caused the change in treatment plan nor whether the differential treatment based on SNRB results improved patient outcomes.

We are not aware of any studies that have evaluated the potential cost-effectiveness of diagnostic SNRBs in patients considered for decompressive lumbar surgery. Primary excision of lumbar intervertebral disc procedures involve a mean inpatient stay of 3.2 days, totalling 30,738 days in English NHS hospitals annually. These acute costs, combined with additional NHS costs and productivity losses associated with rehabilitation from surgery, suggest that a minimally invasive test that accurately differentiates patients who will or will not benefit from surgery has the potential to be cost-effective.

Objectives

This evidence synthesis aims to determine whether selective nerve root blocks (SNRBs) result in more accurate diagnosis in patients considered for lumbar decompression surgery where there is doubt about the localisation of the lesion based on clinical signs and imaging findings (e.g. MRI). An economic model will evaluate the extent to which improvements in diagnostic accuracy lead to more cost-effective care for this patient group and subgroups within it. Specifically, the project will address the following objectives:

1. Systematic review to determine the relative diagnostic and prognostic performance of SNRB in addition to clinical and imaging findings to identify patients with lumbar radiculopathy who are good candidates for lumbar decompression surgery.
2. Evaluate whether the diagnostic and prognostic utility of SNRB varies by patient subgroups (e.g. patients with suspected radiculopathy at more than 1 level of the lumbar spine).
3. Systematic review to summarise the evidence on the incidence of procedure related complications of SNRB.
4. Review of previous economic studies of the use of SNRB in patients with suspected lumbar radiculopathy and a cost-effectiveness model to evaluate the efficiency of using SNRB in patients with discordant clinical and imaging findings, including value of information analysis.

Methods

Systematic review

A systematic review of the literature will be undertaken to determine the accuracy of SNRB in the diagnostic work-up of patients with suspected lumbar radiculopathy, who are candidates for decompressive surgery. The systematic review will be undertaken in accordance with the Centre for Reviews and Dissemination (CRD) guidelines for undertaking systematic reviews[15], and the Cochrane Handbook for Test Accuracy Reviews[16]. Using the same search strategy, we will separately identify studies reporting the incidence of adverse events associated with lumbosacral SNRB.

Search strategy and scoping exercise

A database of published and unpublished literature will be assembled from systematic searches of electronic sources, hand searching, and consultation with experts in the field. Studies will be identified by searching the following major medical databases: MEDLINE, EMBASE, Science Citation Index, BIOSIS Previews and LILACS. In addition, information on studies in progress, unpublished research or research reported in the grey literature will be sought from a range of relevant databases including Inside Conferences, Dissertation Abstracts and NTIS. Internet searches will also be carried out using Google Scholar. Attempts to identify further studies, including unpublished studies, will be made by contacting clinical experts and examining the reference lists of all retrieved articles. A draft search strategy was devised for MEDLINE in the OvidSP interface. The strategy combines terms for the selective nerve root blocks with terms for low back pain. We have not used a diagnostic filter due to problems associated with their use[17] and a desire to identify studies of SNRB related adverse events. The strategy will be validated further to ensure that it identifies all primary studies identified by previous literature reviews. The strategy will be converted to run appropriately on other databases. We will also use previous systematic reviews as a source of studies.

Planned inclusion/exclusion criteria

Studies that fulfil the following criteria will be eligible for inclusion in the systematic reviews:

	Review of diagnostic accuracy	Review of procedure related complications	Review of economic evaluations
Population	Patients with low back pain and symptoms in a lower limb	Patients with low back pain and symptoms in a lower limb	Patients with low back pain and symptoms in a lower limb
Target condition	Lumbar radiculopathy	Lumbar radiculopathy	Lumbar radiculopathy
Index test	Diagnostic SNRB administered under radiological guidance	Diagnostic SNRB administered under radiological guidance	Diagnostic SNRB administered under radiological guidance
Reference standard	Any reported reference standard, e.g. surgical findings and/or clinical outcomes	N/A	N/A
Outcome(s)	Sufficient data to construct contingency tables of index test versus reference standard. Data will be extracted at the patient level, unless unavailable, and then injection level will be used.	Transient and permanent adverse events	Cost effectiveness, cost utility, cost benefit, cost consequence
Study design	Diagnostic cohort or within-patient case-control studies	Any study design except case-reports on which included less than 15 patients.	RCTs, controlled studies, decision analyses

Our scoping exercise suggested that several reference standards (e.g. surgical findings, pain response to active and control SNRB injection) had been used in the literature, but that there is no agreed gold standard. We will include all diagnostic accuracy studies in our narrative systematic review which will allow a broad critique of the strengths and weaknesses of each reference standard reported in this literature.

Assessing relevance and inclusion

The results of the searches will be screened for relevance independently by two reviewers. Disagreements will be resolved through consensus or referral to a third reviewer where necessary. Studies that appear potentially relevant will be ordered and assessed for inclusion by one reviewer and checked by a second.

Data extraction

Data extraction forms will be developed using Microsoft Access. These will be piloted on a small selection of studies and adjusted as necessary. Study data will be extracted by one reviewer and checked by a second. Disagreements will be resolved through consensus or referral to a third reviewer where necessary. Data will be extracted on the following: study details (identifier, study design, location, year), participant details (number of participants, age, gender, details of previous tests received, other relevant details), index test details, comparator test details (where reported), reference standard details and contingency tables of test performance. We anticipate that most diagnostic accuracy studies will present data only on SNRB. However, where presented, we will also record the diagnostic accuracy of clinical findings and imaging findings (e.g. CT myelography or MRI) alone or in combination with SNRB. Data will be extracted and analysed at the patient level (unless unavailable, and then injection level will be used). Where injection level data are used we will use an approximate correction to the standard errors if necessary to avoid overstating precision and giving disproportionate weighting such studies. For the review of adverse events, we will abstract data on the type, number, severity and duration (acute/chronic) of adverse events.

Quality assessment

Diagnostic accuracy studies will be assessed for methodological quality using an updated version of the QUADAS tool [18]. This tool includes domains on patient selection, index test, reference standard, and patient flow and timing and assesses primary studies in terms of risk of bias and applicability to the review question. Quality assessment forms will be developed using Microsoft Access. Quality assessment will be carried out independently by two reviewers. Disagreements will be resolved through consensus or referral to a third reviewer where necessary.

Statistical analysis

The statistical analysis will in general follow the recommendations in Chapter 8 of the draft Cochrane Handbook for Test Accuracy Reviews[16]. Prior to data synthesis, the project team will meet to review all reference standards reported in the literature. The project team will create a hierarchy of reference standards from most to least valid. Diagnostic accuracy studies using reference standards considered invalid will be described and critiqued, but not included in the evidence synthesis. Our recommendations for current practice will be based on studies using the best available reference standards. The range in sensitivity, specificity, likelihood ratios (of both positive and negative tests results) and diagnostic odds ratios (DORs) will be calculated and discussed, together with possible ranges in positive and negative predictive values which will be calculated based on a number of different estimates of disease prevalence. Confidence intervals for sensitivity, specificity, likelihood ratios and DORs in individual studies will be displayed using forest plots. We will stratify our analysis by study design (case control versus cohort) as the potential biases associated with case control studies on this topic (e.g. spectrum bias) are very different to the potential biases in the cohort studies (e.g. partial verification bias).

To assess whether results vary, results will be stratified according to relevant patient subgroups reported either within or between studies. A priori patient subgroups of interest are patients with suspected single versus multi-level radiculopathy and patients with suspected disc versus bony stenosis of the neural foramen. The policy implications of using SNRB in each patient subgroup will be assessed by developing separate cost-effectiveness models for each subgroup using subgroup specific estimates of SNRB sensitivity and specificity.

The extent of data pooling and meta-analysis will depend on the number of sufficiently homogenous diagnostic accuracy studies identified. If meta-analysis is feasible, summary ROC plots (SROC plots) will be used to display sensitivity and specificity using different symbols or separate plots for different test types or combinations of tests. Formal analyses will use bivariate and hierarchical summary ROC (HSROC) models, which the applicants have shown to be identical in the absence of covariate effects[19]. These statistically rigorous approaches allow estimation of summary sensitivity, specificity, likelihood ratios and DORs with associated confidence intervals or regions.

They also allow estimation of summary ROC curves and prediction regions for the true sensitivity and specificity in a future study.

Most of the analysis will be conducted in Stata version 10, using a command for meta-analyses of test accuracy studies (metandi). We will also use the NLMIXED procedure in SAS for the HSROC model with covariates if required.

Adverse events associated with SNRB will be classified as temporary or permanent. The type and frequency of adverse events will be calculated and discussed. Estimates and confidence intervals for complication rates in individual studies will be displayed using forest plots.

Review of previous economic studies

The search strategy for identifying SNRB diagnostic accuracy studies will also be used to identify studies investigating the cost and outcomes of diagnostic SNRB. Titles and abstracts will be reviewed, focussing on economic evaluations of SNRBs in patients with radiculopathy considered for decompressive surgery.

The quality of any primary economic evaluations identified will be assessed using the Quality of Health Economic Studies (QHES) instrument [20]. We will use the Philips checklist [21] to describe the strengths and weaknesses of existing cost-effectiveness decision analysis models. We will provide a qualitative summary of the findings of all previous economic evaluations. Based on our scoping exercise we anticipate that there will be very few, if any, full economic evaluations, especially in an NHS setting. Therefore, we will develop a decision analytic economic model based on the best evidence on costs, diagnostic accuracy, therapeutic impact and health outcomes.

Development of an Economic Model

A decision analytic model will be developed to estimate the cost-effectiveness of SNRB in patients with suspected lumbar radiculopathy who are thought to be suitable for lumbar decompressive surgery. If the systematic review and meta-analysis reveal important differences in the diagnostic accuracy of SNRB by patient subgroup, we will develop separate models for each subgroup (e.g. multiple versus single-level radiculopathy). In developing the model, we will follow the best-practice principles suggested by Buxton and colleagues[22]: 1) The model will be kept as simple as possible to aid understanding by decision makers; 2) The presentation of methods and results will be as transparent as possible; 3) The quality of all data used in the model will be explicitly discussed; 4) Uncertainty in the model will be explored using probabilistic sensitivity analysis; 5) The model will be validated against other models and epidemiological studies.

Additional literature searches will be undertaken to help populate the decision model. We anticipate that the key parameters in the model will include: 1) the pre-SNRB prevalence of nerve root compression; 2) the cost of SNRB; 3) SNRB related complications; 4) the sensitivity and specificity of SNRB; 5) the impact of the SNRB result on the decision to perform surgery or the surgical approach selected; 6) the cost of surgery and conservative care; 7) the effectiveness (quality adjusted life years) of surgical and conservative therapy at reducing morbidity in patients with true positive, false positive, true negative and false negative SNRB test results; and 8) productivity losses to society due to symptom related incapacity.

Some of the model parameters, for example prevalence, SNRB complications and diagnostic accuracy, will be directly informed by our systematic reviews. For other parameters, such as the cost of SNRB and therapy, we will use routine data (e.g. NHS reference costs) and information from NHS acute trust finance departments to derive a range of cost estimates. The primary analysis of the effectiveness of surgical and conservative therapy will be based on EQ-5D outcomes reported in the SPORT RCTs[7]. Because substantial non-compliance with random allocation affected the SPORT results, we will conduct separate sensitivity analyses using both the 'as treated' and 'intention-to-treat' effect sizes. We will access SPORT data under the NIH data sharing guidelines.

In the primary analysis, we will calculate cost-effectiveness from the perspective of the NHS and Personal Social Services, excluding costs incurred by patients, employers and other agencies. Secondary analysis will broaden this to the societal perspective. We will compare the incremental cost effectiveness adding SNRB to the standard diagnostic workup of clinical findings and radiological imaging. The project economists and clinicians will jointly review the structure of the final model to ensure that it reflects the most clinically plausible diagnostic and therapeutic transitions. Extreme value sensitivity analyses will be used to test the internal consistency of the model. The model will consist of two parts. The first (short-run) sub-model will consider the incremental cost per correct diagnosis of SNRB. The short-run model will incorporate point estimates of diagnostic accuracy and a distribution reflecting the range of parameter uncertainty from the systematic review. Estimates of sensitivity and specificity will be combined with the pre-test prevalence of true nerve root compression to generate post-test probabilities of appropriate surgery. This results in four possible short-run outcomes: positive SNRB result in a patient with radiculopathy caused by nerve root compression (true positive), positive SNRB result in a patient whose symptoms are not caused by nerve root compression (false positive), negative SNRB result in a patient with radiculopathy caused by nerve root compression (false negative), and negative SNRB result in a patient whose symptoms are not caused by nerve root compression (true negative).

The second (long-run) element of the model will extrapolate the long-term costs and health effects of SNRB. The long-run model will use a decision tree and Markov process to track the transition of patients between various post-treatment health states (e.g. Good/moderate/poor outcome and death), return to work and the requirement for further therapy (e.g. re-operation). All parameters will be entered into the model as point estimates with distributions reflecting the degree of statistical certainty based on current evidence. The model will initially track costs and outcomes over a four year time horizon to match the outcomes time frame reported by the SPORT trial and then extrapolate over a longer term based on several assumptions about the continuation of the benefit of surgery after the end of the SPORT trial. Costs and outcomes in future years will be discounted at an annual rate of 3.5% and varied between 0% and 6% in sensitivity analysis to account for methodological uncertainty. The main outcome of the model will be the incremental cost per Quality Adjusted Life Year (QALY) of using SNRB in addition to clinical findings and imaging. Probabilistic sensitivity analysis (PSA) will be undertaken to reflect all parameter uncertainty in the model using Monte Carlo simulation. Results will be plotted on the cost-effectiveness plane and expressed using cost-effectiveness acceptability curves and net monetary benefit.

Expected Value of Information (EVI)

The systematic review and economic model will be used to make recommendations for optimal use of SNRB based on current evidence. But evidence is incomplete and further research may be valuable. Expected value of information analysis (EVI) uses the best available evidence (and the uncertainty that surrounds it) to estimate the expected benefit of future research[23]. Research recommendations (and funding decisions) can then focus on research areas where the benefits of future research, by reducing uncertainty, most clearly outweigh the costs of that research. We will use Monte Carlo simulation to obtain EVI estimates from the decision analysis model on the partial expected value of perfect information (pEVPI) and partial expected value of sampled information (pEVSI)[24]. The former estimates whether any amount of further research on a topic (e.g. the sensitivity and specificity of SNRB) is likely to change the optimal diagnostic strategy. The latter estimates the expected benefit of conducting a new research project (e.g. diagnostic accuracy study of SNRB) with a given sample size. EVSI can be compared between different types of research (e.g. a diagnostic accuracy study of SNRB versus an RCT of lumbar discectomy) to establish priorities.

Project Timetable and Milestones

Project start	Month 1	Oct, 2010
Protocol development	Month 1	Oct
Literature searching (including economic data)	Months 2–5	Nov–Feb
Develop economic model structure(s) for review	Months 1–4	Oct–Jan
Protocol peer review	Month 2	Nov
Relevance screening	Months 4 and 5	Jan–Feb
Inclusion assessment	Months 6 and 7	Mar–Apr
Populate economic model with parameters	Months 5–7	Feb–Apr
Data extraction and quality assessment	Months 7 and 8	Apr–May
Systematic Review and Meta-analysis	Months 9–11	Jun–Aug
De-bug economic model, conduct SA and EVI analysis	Months 9–13	June–Oct
Report production	Months 13–15	Oct–Dec
Draft report to advisory panel	End of Month 14	Nov 30, 2011
Deadline for comments on report from advisory panel	Middle Month 15	Dec 15, 2011
Submit final report	End of Month 15	Dec 31, 2011

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