Health Technology Assessment 2009; Vol. 13: No. 17

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EL Simpson, A Duenas, MW Holmes, D Papaioannou and J Chilcott

March 2009
DOI: 10.3310/hta13170

Health Technology Assessment
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Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation

EL Simpson,* A Duenas, MW Holmes, D Papaioannou and J Chilcott

School of Health and Related Research (ScHARR), The University of Sheffield, UK

*Corresponding author

Declared competing interests of authors: none known

Declared competing interests of clinical advisors: All clinical advisors have taken part in advisory groups/symposia/lectures which have been sponsored by various manufacturers for which honoraria have sometimes been received. S. Eldabe and S. Thompson were involved in the PROCESS trial. B. Simpson has in the past received payment from Advanced Neuromodulation Systems for the design of an electrode for spinal cord stimulation, a product which is no longer in production.

Published March 2009

DOI: 10.3310/hta13170

This report should be referenced as follows:

Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess* 2009;**13**(17).

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

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The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 07/08/01. The protocol was agreed in September 2007. The assessment report began editorial review in March 2008 and was accepted for publication in August 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NCCHTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

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Abstract

Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation

EL Simpson,* A Duenas, MW Holmes, D Papaioannou and J Chilcott

School of Health and Related Research (ScHARR), The University of Sheffield, UK

*Corresponding author

Objectives: This report addressed the question 'What is the clinical and cost-effectiveness of spinal cord stimulation (SCS) in the management of chronic neuropathic or ischaemic pain?'

Data sources: Thirteen electronic databases [including MEDLINE (1950–2007), EMBASE (1980–2007) and the Cochrane Library (1991–2007)] were searched from inception; relevant journals were hand-searched; and appropriate websites for specific conditions causing chronic neuropathic/ischaemic pain were browsed. Literature searches were conducted from August 2007 to September 2007.

Review methods: A systematic review of the literature sought clinical and cost-effectiveness data for SCS in adults with chronic neuropathic or ischaemic pain with inadequate response to medical or surgical treatment other than SCS. Economic analyses were performed to model the cost-effectiveness and cost–utility of SCS in patients with neuropathic or ischaemic pain.

Results: From approximately 6000 citations identified, 11 randomised controlled trials (RCTs) were included in the clinical effectiveness review: three of neuropathic pain and eight of ischaemic pain. Trials were available for the neuropathic conditions failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type I, and they suggested that SCS was more effective than conventional medical management (CMM) or reoperation in reducing pain. The ischaemic pain trials had small sample sizes, meaning that most may not have been adequately powered to detect clinically meaningful differences. Trial evidence failed to demonstrate that pain relief in critical limb ischaemia (CLI) was better for SCS than for CMM; however, it suggested that SCS was effective in delaying refractory angina pain onset during exercise at short-term follow-up, although not more so than coronary artery bypass grafting (CABG) for those patients eligible for that surgery. The results for the neuropathic pain model suggested that the cost-effectiveness estimates for SCS in patients with FBSS who had inadequate responses to medical or surgical treatment were below £20,000 per quality-adjusted life-year (QALY) gained. In patients with CRPS who had had an inadequate response to medical treatment the incremental cost-effectiveness ratio (ICER) was £25,095 per QALY gained. When the SCS device costs varied from £5000 to £15,000, the ICERs ranged from £2563 per QALY to £22,356 per QALY for FBSS when compared with CMM and from £2283 per QALY to £19,624 per QALY for FBSS compared with reoperation. For CRPS the ICERs ranged from £9374 per QALY to £66,646 per QALY. If device longevity (1 to 14 years) and device average price (£5000 to £15,000) were varied simultaneously, ICERs were below or very close to £30,000 per QALY when device longevity was 3 years and below or very close to £20,000 per QALY when device longevity was 4 years. Sensitivity analyses were performed varying the costs of CMM, device longevity and average device cost, showing that ICERs for CRPS were higher. In the ischaemic model, it was difficult to determine whether SCS represented value for money when there was insufficient evidence to demonstrate its comparative efficacy. The threshold analysis suggested that the most favourable economic profiles for treatment with SCS were when compared to CABG in patients eligible for percutaneous coronary intervention (PCI), and in patients eligible for CABG and PCI. In these two cases, SCS dominated (it cost less and accrued more survival benefits) over CABG.

Conclusions: The evidence suggested that SCS was effective in reducing the chronic neuropathic pain of FBSS and CRPS type I. For ischaemic pain, there may need to be selection criteria developed for CLI, and SCS may have clinical benefit for refractory angina short-term. Further trials of other types of neuropathic pain or subgroups of ischaemic pain, may be useful.

Contents

Glossary and list of abbreviations

Glossary

Angina pectoris Ischaemic chest pain (usually as the result of coronary heart disease).

Complex regional pain syndrome Neuropathic pain syndrome comprising regional pain, and oedema/vasomotor/sudomotor dysfunction, following noxious event or nerve injury.

Critical limb ischaemia Ischaemic pain manifestation of peripheral arterial disease, with chronic ischaemic rest pain or ischaemic skin lesions.

Failed back surgery syndrome Neuropathic and nociceptive low back and leg pain which has failed to respond to anatomically successful surgical treatment.

Ischaemic pain Pain occurring when there is insufficient blood flow for the metabolic needs of an organ.

Neuropathic pain Pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous systems.

Paraesthesia An abnormal sensation, whether spontaneous or evoked, that is not unpleasant.

Refractory angina Frequent angina attacks uncontrolled by optimal drug therapy/surgery.

Spinal cord stimulation Stimulating the dorsal columns of the spinal cord with an implanted device (spinal cord stimulator) with the aim of modifying perception of neuropathic and ischaemic pain.

List of abbreviations

ABI	ankle to brachial pressure index
ABHI	Association of British Healthcare Industries
BPS	British Pain Society
CABG	coronary artery bypass grafting
CLI	critical limb ischaemia
CMM	conventional medical management
CRPS	complex regional pain syndrome
EFNS	European Federation of Neurological Societies
EQ5D	EuroQol 5D
FBSS	failed back surgery syndrome
GPE	global perceived effect
GTN	glyceryl trinitrate
HES	hospital episode statistics
HRQoL	health-related quality of life
IASP	International Association for the Study of Pain
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
LYG	life-years gained
MQS	Medication Quantification Scale
NHP	Nottingham Health Profile
NSUKI	Neuromodulation Society of UK and Ireland
PCI	percutaneous coronary intervention
PMR	percutaneous myocardial revascularisation
PT	physical therapy
QALY(s)	quality-adjusted life-year(s)
RCT	randomised controlled trial
RD	risk difference
RR	relative risk
SCS	spinal cord stimulation
SF-36	Short Form 36
SIP	Sickness Impact Profile
$TcPo_2$	transcutaneous oxygen pressure
TENS	transcutaneous electrical nerve stimulation
VAS	visual analogue scale

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 in the notes at the end of the table.

Executive summary

Background

Chronic pain is a cause of physical and emotional suffering. Spinal cord stimulation (SCS) modifies the perception of pain by stimulating the dorsal columns of the spinal cord, and may relieve neuropathic or ischaemic pain.

Objectives

This report addressed the question 'What is the clinical and cost-effectiveness of spinal cord stimulation in the management of chronic neuropathic or ischaemic pain?'

Methods

A systematic review of the literature sought clinical and cost-effectiveness data for SCS in adults with chronic neuropathic or ischaemic pain with inadequate response to medical or surgical treatment other than SCS. Comparators were medical or surgical treatment appropriate to condition. Thirteen electronic databases were searched from inception, including MEDLINE (1950–2007), EMBASE (1980–2007) and the Cochrane Library (1991–2007). In addition, relevant journals were hand-searched and appropriate websites for specific conditions causing chronic neuropathic/ischaemic pain were browsed. Clinical outcomes sought included pain, health-related quality of life (HRQoL) and adverse effects. Data were available from randomised controlled trials (RCTs) and were included. Heterogeneity precluded meta-analysis, so a narrative synthesis was presented.

Economic analyses were performed to model the cost-effectiveness and cost–utility of SCS in patients with neuropathic or ischaemic pain.

In patients with neuropathic pain, a two-stage model was developed to explore the cost and health outcomes associated with a 15-year time period of treatment using a UK NHS perspective. A decision tree was used to model the first 6 months of treatment. The decision tree model was extended by a Markov model used to determine the cost and health outcomes over a 15-year time horizon. Data from RCTs were used to determine efficacy and results were presented in terms of incremental cost-effectiveness ratios (ICERs). The model evaluated the cost-effectiveness of treatment in two indications: failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type I. For FBSS there were two comparators, conventional medical management (CMM) and reoperation. For CRPS the comparator was CMM. Detailed reviews were undertaken to obtain the most recent evidence on costs and utility measures for the different health states modelled. UK-specific data were used.

For ischaemic pain, a mathematical model was developed to explore the cost and health outcomes of SCS in refractory angina using a UK NHS perspective. The analysis estimated the ICERs of SCS plus CMM in comparison with coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or CMM. A threshold analysis was presented because of the dearth of direct clinical evidence. This analysis attempted to clarify the impact of overall survival benefit of SCS on cost-effectiveness and cost–utility levels of acceptability.

Results

From approximately 6000 citations identified, 11 RCTs were included in the clinical effectiveness review: three of neuropathic pain and eight of ischaemic pain. Comparators were relevant to UK practice. Good quality, adequately powered trials were available for the neuropathic conditions FBSS and CRPS type I, and they suggested that SCS was more effective than CMM or reoperation in reducing pain. The main limitation of the ischaemic pain trials was small sample sizes, meaning that most of the trials may not have been adequately powered to detect clinically meaningful differences. Trial evidence failed to demonstrate that pain relief in critical limb ischaemia (CLI) was better for SCS than for CMM. Trial evidence suggested that SCS was effective in delaying refractory angina pain onset during exercise at

short-term follow-up, although not more so than CABG for those patients eligible for that surgery, although SCS was a relatively safe alternative to CABG. Complication rates varied across trials, but were usually minor.

The results for the neuropathic pain model, over a 15-year time horizon, a device longevity of 4 years and a device cost of £7745, suggested that the cost-effectiveness estimates for SCS in patients with FBSS who had inadequate responses to medical or surgical treatment were below £20,000 per quality-adjusted life-year (QALY) gained. In patients with CRPS who had had an inadequate response to medical treatment the ICER was £25,095 per QALY gained.

When the SCS device costs varied from £5000 to £15,000, the ICERs ranged from £2563 per QALY to £22,356 per QALY for FBSS when compared with CMM and from £2283 per QALY to £19,624 per QALY for FBSS compared with reoperation. For CRPS the ICERs ranged from £9374 per QALY to £66,646 per QALY.

If device longevity (1 to 14 years) and device average price (£5000 to £15,000) were varied simultaneously, ICERs were below or very close to £30,000 per QALY when device longevity was 3 years and below or very close to £20,000 per QALY when device longevity was 4 years. Sensitivity analyses were performed varying the costs of CMM, device longevity and average device cost, showing that ICERs for CRPS were higher.

In the ischaemic model, it was difficult to determine whether SCS represented value for money when there was insufficient evidence to demonstrate its comparative efficacy. The threshold analysis suggested that the most favourable economic profiles for treatment with SCS were when compared to CABG in patients eligible for PCI, and in patients eligible for CABG and PCI. In these two cases, SCS dominated (it cost less and accrued more survival benefits) over CABG.

Discussion

Clinical effectiveness was demonstrated for SCS over CMM in reducing pain for FBSS and CRPS type I, from good-quality trials. It is unclear whether this can be generalised to other forms of neuropathic pain. Evidence from small trials failed to demonstrate that pain relief in CLI was better for SCS than for CMM, and suggested that SCS was effective in delaying angina pain onset short-term. Trials of other types of neuropathic pain, or subgroups of ischaemic pain, may be useful.

Conclusions

Evidence suggested that SCS was effective in reducing the chronic neuropathic pain of FBSS and CRPS type I. For ischaemic pain, there may need to be selection criteria developed for CLI, and SCS may have clinical benefit for refractory angina in the short term.

Chapter 1
Background

Description of health problem

Chronic pain is defined by its duration. The International Association for the Study of Pain (IASP) defines chronic pain as persisting beyond normal tissue healing time, assumed to be 3 months.[1] This definition comprises continuous pain; however, chronic pain has been otherwise defined as being either continuous or intermittent.[2] In addition to its duration and lack of associated observed pathology, chronic pain is frequently identified by an unpredictable prognosis and may include varying amounts of disability, from none to severe. It is often accompanied by psychological problems, particularly depression and anxiety,[3] although any causal link between these is not fully understood.

Neuropathic pain is defined by IASP as pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous systems.[4] The mechanisms involved in neuropathic pain are complex and involve both peripheral and central pathophysiological phenomena. Types of chronic neuropathic pain include: failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), phantom limb pain, central pain (e.g. post-stroke pain), diabetic neuropathy and post-herpetic neuralgia.

The condition FBSS is clinically defined as persistent or recurrent pain, mainly in the lower back and legs, after technically and anatomically successful lumbosacral spine surgery.[5] It is sometimes referred to as persistent pain following (technically satisfactory) surgery. FBSS comprises both neuropathic and nociceptive pain. Nociceptive pain is caused by an injury to body tissues, and is outside the scope of this report.

Complex regional pain syndrome (which has been called chronic reflex sympathetic dystrophy, or reflex sympathetic dystrophy syndrome, or causalgia) is divided into two types. IASP has defined CRPS type I as usually following an initiating noxious event or period of immobilisation and satisfying the three criteria:

- continuing pain, allodynia (lowered pain threshold) or hyperalgesia (increased pain response)
- oedema (accumulation of tissue fluid), changes in skin blood flow, or abnormal sudomotor activity (nerves that stimulate sweat glands) in region of pain
- no existing conditions that would otherwise account for the degree of pain and dysfunction.[4]

CRPS type II follows nerve injury. IASP defines it as satisfying the three criteria:

- continuing pain, allodynia, or hyperalgesia after nerve injury, usually but not necessarily limited to the distribution of the injured nerve;
- oedema, changes in skin blood flow, or abnormal sudomotor activity in region of pain;
- no existing conditions that would otherwise account for the degree of pain and dysfunction.[4]

Ischaemic pain occurs when there is insufficient blood flow for the metabolic needs of an organ. The pain can be severe and is commonly felt in the legs, but could occur elsewhere. The pain of a heart attack is an example of ischaemic pain. Types of ischaemic pain include critical limb ischaemia (CLI) and angina.

Critical limb ischaemia has been defined by the Trans-Atlantic Inter-Society Consensus on the Management of Peripheral Arterial Disease (TASC) as a manifestation of peripheral arterial disease that describes patients with typical chronic ischaemic rest pain or patients with ischaemic skin lesions, either ulcers or gangrene, with symptoms for more than 2 weeks.[6] Peripheral arterial disease is classified according to Fontaine's stages or Rutherford's categories, ranging in severity from asymptomatic to ulceration/gangrene/major tissue loss.[6] CLI is associated with reduced peripheral blood pressure.[7]

Angina pectoris is ischaemic chest pain. Angina usually occurs in patients with coronary heart disease, involving at least one large epicardial

artery, but can occur in persons with valvular heart disease, hypertrophic cardiomyopathy and uncontrolled hypertension.[8] Angina may not always be of ischaemic origin; it can be the result of Syndrome X, in which the coronary vessels appear normal. Refractory angina is a chronic condition in which frequent angina attacks occur despite optimal drug therapy/surgery. Angina pain typically occurs during exercise. The New York Heart Association defines cardiac disease in terms of functional capacity and objective assessment, with functional capacity ranging from Class I – cardiac disease without resulting limitation of physical activity, to Class IV – inability to carry on any physical activity without discomfort.[9] A similar classification is available from the Canadian Cardiovascular Society.[10]

Prevalence

Published estimates of the prevalence of any chronic pain (that is, not restricted to neuropathic and ischaemic pain) vary widely. Elliott *et al*.,[2] reporting a range from 2% to 45%, suggest that some of this variation can be ascribed to poor instruments, inadequate study size and studies concentrating on specific diagnoses within chronic pain. Their own study in the Grampian region of the UK reported a prevalence of 50.4% among adults. Overall prevalence increased with age (from around 30% of those aged 25–34 years to around 60% in those older than 65 years). The two commonest causes of pain were back pain (16%) and arthritis (16%). Back pain varied little with age, while arthritis and angina (4.5% of sample) both increased consistently with age. Severe chronic pain was reported by 10.8% of respondents.

Restricting to pain of neuropathic origin, the prevalence of chronic neuropathic pain has been estimated by the Neuropathic Pain Network (2004) to be 3 million people, or 7.5%, in the United Kingdom.[11] A study conducted in the UK suggested the prevalence of chronic neuropathic pain to be 8.2%.[12]

A study from Norway looked at chronic critical lower limb ischaemia in a population aged from 40 to 69 years, and found the prevalence to be 0.24%, with some increase with increasing age.[13] A UK study of men aged 40 to 59 years found a prevalence of definite angina of 4.8%, and of possible angina for a further 3.1% of all men.[14]

Impact of health problem

Chronic pain is an important cause of physical and emotional suffering, familial and social disruptions, disability and work absenteeism. Breivik *et al*.[15] conducted a European survey of chronic pain (including but not limited to neuropathic pain), in 15 European countries and Israel showing that 19% of adults suffer chronic pain of moderate to severe intensity. In interviews with 4839 patients, it was found that chronic pain had a severe impact on the following daily activities: sleeping, exercising, lifting, household chores, walking, attending social activities, working outside the home, maintaining an independent lifestyle, having sexual relations, driving and maintaining relationships with family and friends. For instance, 32% of the respondents were no longer able to work outside their homes while 34% of the respondents were less able to attend social activities, and 65% were less able or unable to sleep.

Breivik *et al.*[15] also reported that of 300 respondents in the UK, 32% suffered severe pain (8, 9 or 10 on the 1–10 Numeric Rating Scale). As a result of their pain, 25% had lost their job, 16% had changed job responsibilities and 18% had changed jobs entirely. The ability to work of people who suffer chronic pain can have a direct impact on society's economy. In-depth interviews also found that 24% of respondents in the UK had been diagnosed with depression by a medical doctor, showing that pain may have a direct influence on the emotional status of patients.

In a cross-sectional survey (observational), McDermott *et al.*[16] reported the association of neuropathic pain severity using the health-related quality of life instrument EuroQoL-5D (EQ5D).[16] This study considered 602 patients with neuropathic pain in six European countries (France, Germany, Italy, the Netherlands, Spain and the United Kingdom). Pain severity was measured by the Brief Pain Inventory (BPI) pain severity score (range 0–10) and was found to be associated significantly ($p < 0.001$) with poorer EQ5D scores. Scores of 0–3, 4–6 and 7–10 represented mild, moderate and severe pain ratings, respectively. The EQ5D scores were 0.67 for mild, 0.46 for moderate and 0.16 for severe pain. These scores are lower than those for other diseases such as heart attack 0.76[17] and moderate stroke 0.68,[18] showing that neuropathic pain can have a heavy impact on the patients' quality of life.[16]

Measurement of disease

Neuropathic pain tends to be diagnosed by clinical opinion. Ischaemic conditions may have objective clinical measures, such as the Fontaine classification of CLI, which includes diagnosis using the ankle to brachial pressure index, or the objective assessment of the New York Heart Association classification of angina. There are widely used measures of pain and health-related quality of life (HRQoL).

The visual analogue scale (VAS) is a validated, widely used measure of pain intensity. The scale is a line, usually from 0 to 10, with 0 representing 'no pain' and 10 representing 'unbearable pain'. The patient indicates the point on the scale that they feel represents the intensity of their pain.[19,20] Within the context of trials, the cut-off for successful pain relief has sometimes been defined as a 50% or greater reduction in pain from baseline as shown on the VAS. However, given that a lower percentage reduction may be considered clinically beneficial by patients, and that among patients with chronic neuropathic pain treated with pharmacological therapies approximately 30–40% achieve > 50% pain relief,[21,22] it has been suggested that a clinically meaningful reduction of chronic pain in placebo-controlled trials would be a two-point decrease or a 30% reduction on a rating scale from 0 to 10.[21,23]

The McGill Pain Questionnaire is a validated outcome measure for pain.[24] It has two parts, the first with scores from 0 to 20, the second with scores from 0 to 63, with higher scores indicating more pain.[24]

There are many validated measures of HRQoL. Generic measures (that is, those designed to measure any health-related changes in quality of life) include the Nottingham Health Profile (NHP), EQ5D, the Sickness Impact Profile (SIP) and the Short Form 36 (SF-36). The NHP has two parts: part 1 assessing six different dimensions (pain, sleep, energy, mobility, social isolation and emotional behaviour) and part 2 assessing the effects of health on work, home life and relationships.[25–28]

The EQ5D assesses five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[29] The SIP is organised into 12 categories (emotional behaviour, body and movement, social interaction, sleep and rest, home management, mobility, work, recreation, ambulation, alertness behaviour, communication and eating).[30] The SF-36 investigates eight health concepts (physical activities, social activities, limitations in usual role activities because of physical health problems, bodily pain, general mental health, limitations in usual role activities because of emotional problems, energy/fatigue, general health perceptions).[31,32] There are also validated disease-specific measures, such as the Seattle Angina Questionnaire[33] and the Quality of Life Questionnaire Angina Pectoris (QLQ-AP).[34]

Current service provision

Management of chronic pain

Chronic pain can be managed through primary and secondary care. Several therapies can be used in parallel. Pharmacological treatment is primarily the use of analgesics, but can include other medication relevant to the conditions such as non-steroidal anti-inflammatory drugs and anticonvulsants. Where other therapies have failed, intrathecal drug delivery is considered in some centres. Other therapies include physical therapy, and transcutaneous electrical nerve stimulation. Management of patients with pain may include attempts to increase function and coping skills while pain continues. Antidepressants are provided, as depression is often co-morbid with chronic pain although treatment of one condition may not necessarily improve the other. Psychological therapies, including cognitive behavioural therapy and supported self-management, are delivered. The order in which therapies are selected varies across centres in the UK, and different approaches may be delivered in parallel. The British Pain Society (BPS) recommends pain clinics and pain management programmes, and has found that patients with chronic pain have often been to a number of secondary-care specialists before being referred to pain clinics.[35]

There are other possibilities for treatment specific to condition. For neuropathic pain, pharmacotherapy is the favoured treatment, but nerve blocks may be considered. Patients with FBSS may undergo reoperation. For ischaemic conditions, the preferred treatment is revascularisation, for angina this includes coronary artery bypass grafting and percutaneous myocardial revascularisation, for CLI it includes percutaneous angioplasty or distal grafting. However, not all patients with chronic ischaemic pain are eligible for this, for example coronary artery bypass grafting is not considered suitable for refractory angina. For chronic CLI, amputation is often considered. Non-

surgical treatments for CLI are prolonged bed rest and analgesia.

Current service cost

In a European survey, Breivik *et al.*[15] reported that 13% of the respondents in the UK suffered from chronic pain. Although this study considers a very small sample of the UK population, if this figure is applied to 2006 population estimates, it equates to approximately 6.9 million people in England and Wales who suffer chronic pain.[36] In the prevalence estimates reported by Taylor,[37] the neuropathic back and leg pain prevalence in the UK is 5800 per 100,000 population. Therefore, approximately 405,115 people in England and Wales suffer from neuropathic back and leg pain, costing approximately £2 billion a year (from a societal perspective). An estimate of approximately 4051 patients a year would be suitable for spinal cord stimulation (SCS) treatment if just 1% of the estimated chronic pain population were considered to be suitable for SCS in England and Wales.

According to the British Heart Foundation Statistics Database[38] the prevalence of angina is approximately 1.1 million people, representing a cost estimate of £221 million in the UK. Estimates suggest that 5–10% of people who suffer from angina will develop refractory angina.[39] This represents an estimated cost of refractory angina in the UK of between £11 million and £22 million.

In the year 2000 the estimated cost of CLI in the UK was over £200 million a year.[40]

Guidelines

Guidelines from the European Federation of Neurological Societies (EFNS) make an evidence-based recommendation for the use of SCS in FBSS and CRPS type I.[21] They also suggest the need for comparative trials in other indications, although there are reports of positive findings from case series for SCS in CRPS type II, peripheral nerve injury, diabetic neuropathy, post-herpetic neuralgia, amputation pain and partial spinal cord injury.[21]

Detailed guidelines produced by the BPS and the Society of British Neurological Surgeons recommend that SCS should be delivered, with other therapies, through a multidisciplinary pain management team including clinicians experienced in SCS, with ongoing surveillance and support.[35]

These guidelines stress the need for informed consent from patients, and state that SCS is contraindicated in patents with a bleeding disorder, systemic or local sepsis, or a demand pacemaker or implanted defibrillator. Guidelines from the USA suggest that SCS is suitable for patients of either sex and any age (excluding children for whom safety has not been established) although evidence is not firmly established that SCS has equal efficacy across sex and age groups.[41]

Non-SCS guidelines relevant to the treatment of chronic pain include the National Service Framework for long-term conditions,[42] EFNS guidelines on pharmacological treatment of neuropathic pain,[22] and guidelines for pain management services from the from Royal College of Anaesthetists, Royal College of General Practitioners and BPS,[35,43,44] Quality Improvement Scotland,[45] and IASP.[46] Guidelines support a multidisciplinary approach to pain management.

Description of technology under assessment

Spinal cord stimulation has been used since 1967. Currently it is used to treat patients with intractable pain syndromes including the failed back surgery syndrome, complex regional pain syndrome and ischaemic cardiac and limb pain. The precise mechanism of pain modulation is not fully understood. One theory is that it involves direct and indirect inhibition of pain signal transmission, and to have autonomic effects, the technique may inhibit chronic pain by stimulating large diameter afferent nerve fibres in the spinal cord. Pain is masked by the production of numbness/tingling (paraesthesia). It has been speculated that for ischaemic pain SCS gives an additional benefit of redistributing microcirculatory blood flow.[47]

Spinal cord stimulation (also known as dorsal column stimulation) is not curative for the underlying condition, and may not be a stand-alone treatment but is provided within the context of the multidisciplinary care team. Expected benefits of SCS are reduction in pain, improved quality of life and possible reduction in pain medication usage. Reduction in pain may improve sleep and also increase alertness by allowing reductions in drug intake. Improved function (including general activities of daily living and possibly also return to work), may be sought for some conditions, although for some conditions such as FBSS, return to work is considered unlikely.

Spinal cord stimulation modifies the perception of neuropathic and ischaemic pain by stimulating the dorsal columns of the spinal cord. It is not effective for nociceptive pain.[35] SCS is reversible.

The BPS suggests that SCS may be considered when first-line therapies for chronic pain have failed. A typical SCS device has four components:

- an electrical pulse generator or receiver device which is surgically implanted under the skin in the abdomen, in the buttock area or in the lateral chest wall
- implanted leads with a variable number of electrode contacts near the spinal cord
- an extension cable that connects the electrode(s) to the pulse generator
- a hand-held remote controller which the patient uses to turn the stimulator on or off, selecting different programmes, and to adjust the level of stimulation, within limits as prescribed by the physician.

Rechargeable systems also include a charger.

The implantation procedure involves placing leads in the epidural space, and implanting a subcutaneous generator and controller, which allow alteration of parameters such as pulse width, duration and intensity of stimulation. Repetitive electrical impulses are then delivered to the spinal cord.

Pulse generation is achieved with an implantable pulse generator. An alternative form of pulse generation is the radiofrequency receiver. The choice of SCS device depends on individual patient requirements (e.g. pain patterns, power and coverage needs) and preference as well as the physician's preference. A number of SCS devices have received European approval for marketing (CE Marking) and are currently available in the UK. CE marked indications are presented in Appendix 1.

In general, SCS is part of an overall treatment strategy and is used only after the more conservative treatments have failed. However, for indications well-supported by evidence, the BPS suggests that SCS may be considered when simple first-line therapies have failed. The implantation must be performed in an operating theatre suitable for implant surgery. As a long-term therapy for a chronic condition, it also requires appropriate infrastructure and funding for ongoing surveillance and maintenance (e.g. replacing the pulse generator, revising the leads). Positive findings from case series have been reported for SCS in FBSS, CRPS I and II, peripheral nerve injury, diabetic neuropathy, post-herpetic neuralgia, stump or phantom limb pain, partial spinal cord injury, chronic low back pain, chronic back and leg pain, ischaemic limb pain and angina pain.[21,48–52]

Current usage in the NHS

Hospital Episode Statistics for a 12-month period 2005–6 (England)[53] indicate that there were 695 cases of 'Insertion of neurostimulator adjacent to spinal cord', and also 492 cases of 'Attention to neurostimulator adjacent to spinal cord'. For 2006–7 these figures were 645 and 464, respectively.[54] An estimate by the Neuromodulation Society of UK and Ireland[55] suggests that the Hospital Episode Statistics data are an underestimate, and that there have been at least 1000 SCS implants per annum (with an additional 300 replacements) across UK and Ireland.

There are approximately 20–30 centres in the UK that currently offer SCS implantation. There are differences between services in whether surgery is offered as a day case or requires a stay on the ward, whether electrodes are implanted surgically or percutaneously, and whether test stimulation is routinely conducted before permanent implantation of SCS. Test stimulation can investigate the ability of the SCS device to cover the patient's area of pain with the paraesthesia sensation. This coverage may not necessarily be maintained months after the test.

There is no clear evidence indicating if test stimulation can predict how successful pain relief provided by SCS will be long-term. The EFNS suggests that test stimulation is not a guarantee of long-term success, but can identify patients who do not like the sensation or cannot achieve appropriate stimulation.[21]

Opinion is divided about the usefulness of test stimulation as a predictor of treatment effectiveness or as a means of setting parameters for level of stimulation. There are two types of test stimulation, one of which involves completely removing the device after test stimulation then later implanting SCS in patients for whom the test was successful. The other type uses a component from the test stimulation as part of the permanent implant.

Anticipated costs associated with intervention

The estimated number of new patients receiving SCS for the treatment of chronic pain in England in a 12-month period 2006–7 was 645.[54] Assuming an associated cost per implant (e.g. device, intervention duration, inpatient day case, leads cost, reprogramming session) for the first year of approximately £10,000, the total gross cost for SCS in 2007 is expected to be £6.5 million. If an annual growth rate of 10% on the number of patients receiving SCS is assumed the annual cost rises to approximately £20 million by 2011. This estimate is calculated considering the device costs, screening, implantation costs, adverse events and health-care resources used during the patients' management.

It is uncertain at the moment what proportion of the individuals who are eligible for SCS treatment will receive it in the future. If SCS is recommended for the treatment of neuropathic and ischaemic pain then more funding for the provision of chronic pain services in England and Wales may be required.

Chapter 2

Definition of the decision problem

Decision problem

The assessment addressed the question 'What is the clinical and cost-effectiveness of spinal cord stimulation in the management of chronic pain of neuropathic or ischaemic origin?'

The intervention investigated was SCS. Spinal cord stimulator devices comprised spinal cord stimulators with implantable pulse generator systems (non-rechargeable and rechargeable) and spinal cord stimulators with radiofrequency receiver systems. This intervention was compared with medical and surgical treatments (appropriate to condition) that did not include SCS.

The relevant population was adults with chronic neuropathic or ischaemic pain who had had an inadequate response to medical or surgical treatment (appropriate to condition) other than SCS, or who were considered unsuitable for alternative surgical therapy. This review excluded chronic pain that did not encompass pain of neuropathic or ischaemic origin, and so nociceptive pain was excluded.

The outcomes of interest were measures of pain, health-related quality of life, physical and functional abilities, anxiety and depression, medication use, complications and adverse effects (e.g. procedural complications and technical failures).

Overall aims and objectives of assessment

The objectives of the review were:

- to evaluate the clinical effectiveness and side-effects of SCS in terms of pain, health-related quality of life and physical and functional abilities
- to estimate the incremental cost-effectiveness of SCS compared with current standard therapy
- to estimate the potential overall cost to the National Health Service in England and Wales.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Identification of studies

A comprehensive search was undertaken to systematically identify clinical effectiveness literature concerning SCS in adults with chronic neuropathic or ischaemic pain.

The search strategy comprised the following main elements:

- searching of electronic databases
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

The following databases were searched from inception: MEDLINE (1950–2007), EMBASE (1980–2007), CINAHL (1982–2007), BIOSIS (1985–2007), the Cochrane Database of Systematic Reviews (1991–2007), the Cochrane Controlled Trials Register (1991–2007), the Science Citation Index (1900–2007) and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA; all 1991–2007) and OHE HEED (1967–2007). PRE-MEDLINE was also searched to identify any studies not yet indexed on MEDLINE. Current research was identified through searching the National Research Register, the Current Controlled Trials register and the MRC Clinical Trials Register. Sources such as Google Scholar were searched. The tables of contents from key journals were searched online: *Neuromodulation*, *Journal of Neurosurgery*, *British Journal of Neurosurgery*, *Pain*, *European Journal of Pain*. In addition, websites for specific conditions causing chronic neuropathic/ischaemic pain were browsed, e.g. International Research Foundation for Complex Regional Pain Syndrome, International Neuromodulation Society, Neuromodulation Society of UK and Ireland, British Pain Society, European Federation of Chapters of the International Association for the Study of Pain, the European Taskforce guidelines for neurostimulation therapy for neuropathic pain on the European Federation for Neurological Societies website. Any industry submissions, as well as relevant systematic reviews were hand-searched to identify any further clinical trials. Searches were not restricted by language, date or publication type.

The MEDLINE search strategy is presented in Appendix 2.

Literature searches were conducted from August 2007 to September 2007. References were collected in a database, and duplicates were removed.

Inclusion and exclusion criteria

Inclusion criteria

Intervention

- spinal cord stimulator devices.

This included spinal cord stimulators with implantable pulse generator systems (non-rechargeable and rechargeable) and spinal cord stimulators with radiofrequency receiver systems.

Population

- adults with chronic neuropathic or ischaemic pain who have had an inadequate response to medical or surgical treatment (appropriate to condition) other than SCS.

Comparator

- medical and/or surgical treatment (appropriate to condition) that does not include SCS.

Outcomes

- pain
- health-related quality of life
- physical and functional abilities
- anxiety and depression
- medication use
- complications and adverse effects (e.g. procedural complications and technical failures).

Study types

Published papers were assessed according to the accepted hierarchy of evidence, whereby meta-analyses of randomised controlled trials (RCTs) are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative.[56] Data from non-randomised studies were not included because

evidence for relevant populations and outcomes was available from RCTs. Systematic reviews were checked for RCTs that met the inclusion criteria of this review. Systematic reviews not restricted to reviews of only RCTs, were retained for discussion. These included controlled trials and also covered case series. Case series are considered methodologically weak because they lack a control group, so the prognosis in untreated or differently treated patients is unknown and any effect shown cannot be definitely attributed to the treatment alone. They are prone to selection bias and, as with other non-randomised studies, one would expect bias toward positive results.[57]

Exclusion criteria

Trials were excluded if the intervention was neurostimulation that involved stimulation of other parts of the nervous system (e.g. peripheral nerves, deep brain), if patients had prior use of SCS, were pregnant or children, or if the trial was only published in languages other than English.

Based on the above inclusion/exclusion criteria, study selection was made by one reviewer.

Data abstraction, critical appraisal strategy and synthesis

Data were extracted with no blinding to authors or journal. Quality was assessed according to criteria based on NHS CRD Report No.4.[56] The quality assessment form is shown in Appendix 3. The purpose of such quality assessment was to provide a narrative account of trial quality for the reader. Data were extracted by one reviewer using a standardised form (Appendix 5). Pre-specified outcomes were tabulated and discussed within a descriptive synthesis.

Results

Quantity and quality of research available

The search for clinical effectiveness literature yielded 6067 article citations when duplicates had been removed. *Figure 1* shows study selection. Citations presenting purely economic analyses were not included in this chapter. References excluded at the full-paper screening stage, with reason for exclusion, are presented in Appendix 4.

There were 27 references from 11 trials accepted into the review (including the publication of a pilot study of one of the included trials[58]). These comprised three trials[59–67] of neuropathic pain and eight trials[68–84] of ischaemic pain.

There were also 11 references relating to nine relevant systematic reviews. These comprised three reviews of chronic pain,[47,48,85] two reviews of CRPS,[5,50,51] and one review each of FBSS and CRPS[86], FBSS and chronic back/leg pain,[5,49] chronic low back pain[52] and CLI.[87,88]

A summary of included trials is shown in Tables 1 and 2. There were three included trials of neuropathic pain (*Table 1*) and eight included trials of ischaemic pain (*Table 2*). More study details are presented in Appendix 5.

All studies used SCS devices with an implantable pulse generator and a non-rechargeable internal battery; none of the studies used SCS devices with radiofrequency systems. All studies used SCS devices from Medtronic, with the majority using Itrel II or III systems. Studies were sponsored by the industry. It has been reported that studies funded by industry report more favourable results than non-industry-funded studies.[89]

Four of the studies included a test stimulation (PROCESS, North, Kemler, Claeys), whereas the others did not. If test stimulation were an indicator of extent of long-term pain relief, and those failing test stimulation were excluded from a trial, this would be expected to lead to the trial having a larger treatment effect than trials without test stimulation or exclusions. In two trials no participants failing test stimulation were implanted with permanent SCS devices (North 29% failed, Kemler 33% failed), in one trial five of nine participants failing the test stimulation received permanent SCS implants (PROCESS 17% failed), in one trial all those undergoing test stimulation received permanent SCS (Claeys 0% failed). The lower failure rate of the CLI trial is unsurprising because paraesthesia coverage is usually easier to achieve for ischaemic than neuropathic pain. Three of these trials (PROCESS, Kemler, Claeys) included intention-to-treat (ITT) analyses. For the Claeys trial this would be the same as a per treatment analysis because there were no test failures. The PROCESS and Kemler trials reported analyses that analysed patients allocated to SCS in the SCS group regardless of whether the patient had passed or failed test stimulation or received a permanent implant. This indicates that the inclusion of test stimulation in trials was unlikely to skew the results in favour of SCS.

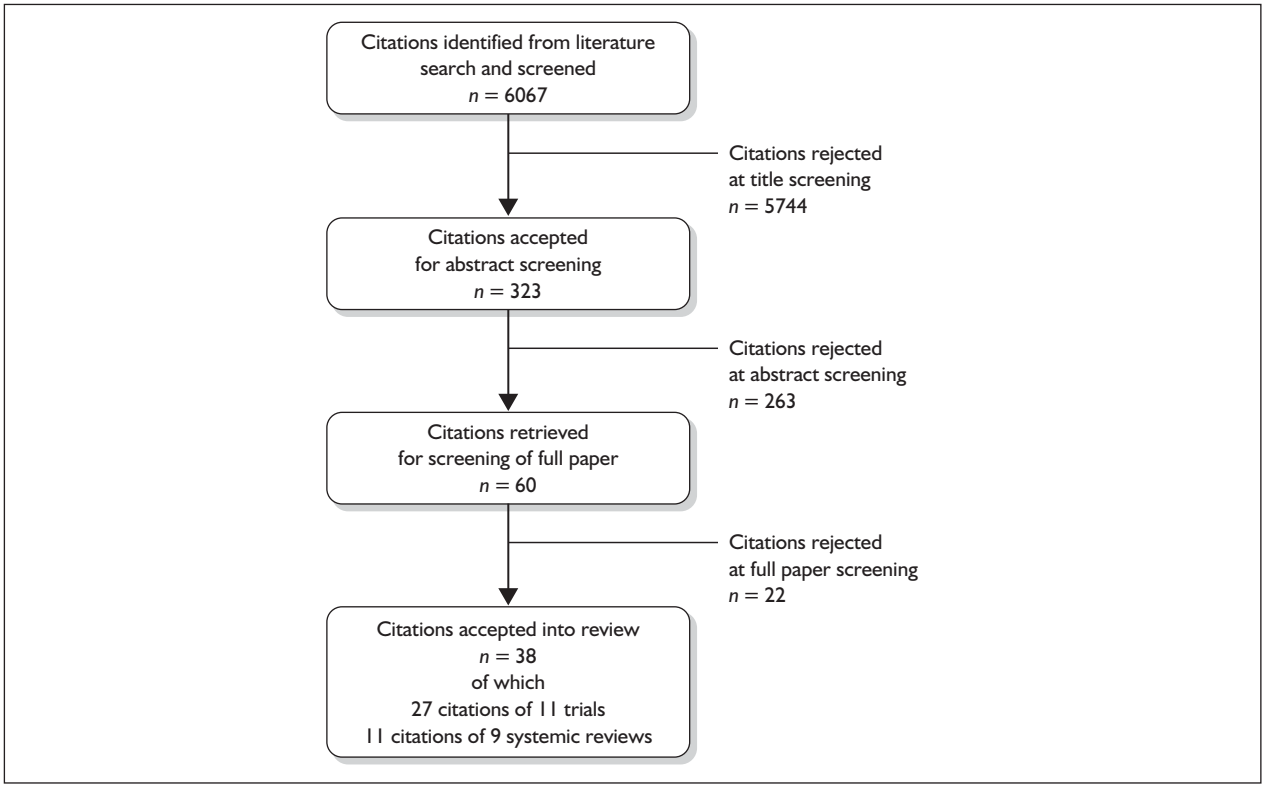

FIGURE 1 *Flow diagram of study selection.*

As can be seen from *Table 1* and *Table 2*, there was substantial heterogeneity of populations and comparators. There were also differences in outcome measures employed. Meta-analyses were precluded in trials of FBSS and angina because of differences in comparators, and there was only one CRPS trial. Trials of CLI had differences in comparators and populations; however, two systematic reviews attempted meta-analyses.

All the included studies were prospective RCTs. With the exception of the Suy trial, which was published as a book chapter, the trials were presented in peer-reviewed journal articles. Four trials (PROCESS, ESES, Suy, Jivegard) were multicentre trials; the other seven were single-centre trials. Trial comparator treatments, including surgical, pharmacological and physical therapies, are all commonly used in the UK.

TABLE 1 *Summary of neuropathic pain trials*

Trial	Indication	Intervention	Comparator	Total number randomised	Data at follow-up	Primary outcome
PROCESS (Kumar *et al*., 2005, 2007;[59,60] Milbouw and Leruth, 2007[61])	Failed back surgery syndrome	SCS plus CMM	CMM	100	6 and 12 months	Proportion of patients achieving at least 50% pain relief in the legs
North (North *et al*., 1994, 1995, 2005[62–64])	Failed back surgery syndrome	SCS plus CMM	Reoperation plus CMM	60	6 months, and mean 2.9 years	At least 50% pain relief plus patient satisfaction
Kemler (Kemler *et al*., 2000, 2004, 2006[65–67])	Complex regional pain syndrome type I	SCS plus physical therapy	Physical therapy	54	6, 24 and 60 months	Visual analogue scale pain intensity change from baseline

TABLE 2 *Summary of ischaemic pain trials*

Trial	Indication	Intervention	Comparator	Total number randomised	Data at follow-up	Primary outcome
ESES (Spincemaille *et al*., 2000;[68,69] Klomp *et al*.,1999;[70] Ubbink *et al*., 1999;[71] Klomp, 1995;[72] pilot study, Spincemaille, 2000[58])	Critical limb ischaemia	SCS plus CMM	CMM	120	6, 12, 18 and 24 months	Limb salvage rates; pain relief
Suy (Suy *et al*., 1974[73])	Critical limb ischaemia	SCS plus CMM	CMM	38	24 months	Limb salvage rates
Jivegard (Jivegard *et al*., 1995[74])	Critical limb ischaemia	SCS plus peroral analgesics	Peroral analgesics	51	18 months	Limb salvage rates
Claeys (Claeys and Horsch, 1997, 1998;[75, 77] Claeys, 1998[78])	Critical limb ischaemia	SCS plus prostaglandin E1	Prostaglandin E1	86	12 months	Limb salvage rates
De Jongste (DeJongste *et al*., 1994[79])	Refractory angina	SCS	No SCS	17	6–8 weeks	Exercise capacity; HRQoL
ESBY (Mannheimer *et al*.,1998;[80] Norrsell *et al*., 2000;[81] Ekre *et al*., 2002[82])	Refractory angina	SCS	Coronary artery bypass surgery	104	6 and 58 months	Angina attacks
SPiRiT (McNab *et al*., 2006[83])	Refractory angina	SCS	Percutaneous myocardial laser revascularisation	68	12 months	Exercise capacity
Hautvast (Hautvast *et al*., 1998[84])	Refractory angina	SCS	Inactive stimulator	25	6 weeks	Exercise capacity

Most of the outcome measures used by the included trials have been validated:

- Visual Analogue Scales (VAS;[19] see Chapter 1, Description of health problem; validity is not universally acknowledged for chronic pain, they may be more applicable to acute pain)
- McGill Pain Questionnaire[90]
- Medication Quantification Scale[91]
- Jebsen functional test for the hand[92]
- Kemler functional test for the foot[93]
- Oswestry Disability Index (ODI)[94]
- Bruce protocol exercise test[95]
- Nottingham Health Profile[25]
- EuroQol 5D[29]
- short generic version Sickness Impact Profile[30]
- generic Short Form 36[31]
- standardised questionnaire scoring Daily activities and Social activities[10]
- Linear Analogue Self-Assessment (LASA) scale[96]
- Seattle Angina Questionnaire[33]
- Quality of life questionnaire Angina Pectoris (QLQ-AP)[34]
- Self-Rating Depression Scale.[97]

Details of quality assessment are presented in Appendix 3.

Inadequate methods of random assignment, inadequate allocation concealment, excluding participants from analysis and lack of blinding can lead to overestimation of treatment effect.[98] Method of randomisation was reported and adequate in five trials (PROCESS, North, Kemler, ESES, SPiRiT). Allocation concealment was reported and adequate in five trials (PROCESS, Kemler, ESES, DeJongste, SPiRiT).

All the trials presented statistical analyses in which patient data were included according to allocated treatment, rather than to received treatment, in accordance with the ITT principle. Most trials presented ITT analyses with imputed data for withdrawals/losses to follow-up. Three trials did not

present ITT (North, ESBY, SPiRiT) although one of these (SPiRiT) reported that ITT was carried out using last observation carried forward, but this analysis was not reported because the authors stated that it did not alter the conclusions although differences between groups were reduced. Trials with patients not receiving allocated treatment, or withdrawals/losses to follow-up, also presented per treatment analyses. A power calculation (for primary outcome measure) was reported and sufficient patients were randomised in six of the trials (PROCESS, North, Kemler, ESES, Jivegard, SPiRiT), although some of these later became underpowered (ESES, Jivegard).[99] Other trials may not have been adequately powered to detect clinically meaningful differences.

Blinding was not included in the quality assessment. None of the trials were blinded. Blinding of patients and clinicians would have been impossible. Trials had no surgery, or different surgery, in the control group, or had an inactive stimulator of which patients would be aware because of the lack of paraesthesia. For most of the outcome measures, the patients themselves were the outcome assessors, which precluded the opportunity for employing independent blinded outcome assessors. Lack of blinding can lead to the placebo effect, which can influence outcome measures with an element of subjectivity for the patient or clinician, such as patient self-reported pain, but is less likely to influence outcome measures with definite clinical indications in the trial protocol, such as decision to amputate. Surgical techniques have been suggested to have strong placebo effects.[100] The placebo effect is potentially strengthened for the trials in which control groups were given treatment which they had previously tried without success.

Clinical effectiveness in neuropathic pain

Two RCTs were available for FBSS and one RCT for CRPS. These trials were designed to assess pain relief.

Systematic reviews identified case series for neuropathic conditions other than FBSS and CRPS. Taking into account the poor quality of studies, and that case series were heterogeneous and difficult to combine,[52] systematic reviews found that SCS was reported as having a favourable effect in the majority of case series for stump or phantom limb pain,[48] peripheral neuropathy,[48] post-herpetic neuralgia,[48] chronic low back pain,[52] chronic back and leg pain,[49] FBSS[49] and CRPS I and II.[48,50,51] A review by Taylor *et al.*[49] found that greater treatment effects of SCS were reported by case series of poorer quality and shorter duration.

Clinical effectiveness in failed back surgery syndrome

The two RCTs of FBSS used different comparators. The comparator in the PROCESS trial was CMM, and the comparator in the North trial was reoperation. Both studies allowed crossover to the other treatment group. Crossover can lead to difficulty in interpreting long-term results.[89] In both trials, SCS was in addition to CMM. Participants in both trials had neuropathic pain of radicular origin and had undergone at least one back surgery. Both trials had adequate methods of randomisation. PROCESS had adequate allocation concealment and presented ITT analysis, whereas the North trial did not. In the North trial baseline details were not presented. In PROCESS baseline comparability was achieved apart from back pain; however the primary outcome of the trial was leg pain and baseline leg pain did not differ between groups. Further details of the trials are presented in Appendix 5.1.

Pain outcomes

Both trials used VAS to measure pain. In the PROCESS trial, leg pain was reduced by 50% or more in significantly more patients in the SCS group than in the CMM group at 6 months ($p < 0.001$) and 12 months ($p = 0.005$). A similar outcome in the North trial, patient satisfaction plus 50% or more pain relief, was achieved by significantly more patients in the SCS group than in the reoperation group ($p = 0.04$). Patient satisfaction was also assessed in the PROCESS trial, with significantly more SCS (66%) than CMM (18%) patients satisfied with pain relief at 6 months ($p < 0.001$). *Table 3* shows ITT/worst-case analyses. The PROCESS trial per treatment analysis at 12 months also showed a significant difference between groups ($p = 0.03$), as did the North trial analysis of patients available for long-term follow-up ($p = 0.01$).

Patient self-reported pain related to daily activities did not differ between the SCS and reoperation groups (North).

Medication outcomes

As shown in *Table 4*, there was no difference between the SCS and CMM groups in opioid use, morphine equivalent dose or non-steroidal antiinflammatories, or antidepressants (borderline significance $p = 0.06$; PROCESS). Significantly fewer SCS than CMM patients were taking

TABLE 3 *Failed back surgery syndrome pain outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis) NB different comparators	VAS 50% or more pain relief SCS group *n* (%)	VAS 50% or more pain relief control group *n* (%)	Comparison
PROCESS	6 months	50	44	24 (48)	4 (9)	OR 9.23 (99% CI 1.99–42.84). $p < 0.001$
PROCESS	12 months	47	41	(34)	(7)	$p = 0.005$
North	Mean 2.9 years	23	26	Plus patient satisfaction; 9 (39)	Plus patient satisfaction; 3 (12)	$p = 0.04$

99% CI, 99% confidence intervals; OR, odds ratio.

anticonvulsants at 6 months ($p = 0.02$) (because of a change in CMM group; PROCESS). The reoperation group required an increase in opiate analgesics significantly more often than the SCS group ($p = 0.025$; North), which may indicate that the difference between groups in pain as measured by the VAS in this trial could have been more pronounced if analgesic use had remained at baseline values.

Functional outcomes

Functional ability at 6 months, as measured by the Oswestry Disability Index (*Table 5*), improved significantly from baseline for the SCS group ($p < 0.001$), but not for the CMM group, with the difference between groups being significant ($p < 0.001$) (PROCESS).

Both trials reported no difference between groups in employment status.

Patient self-report of neurological function (lower extremity strength and co-ordination, sensation, bladder/bowel function) did not differ between SCS and reoperation groups (North).

North reported that patients randomised to reoperation were more likely to cross over to SCS ($n = 14$ out of 26) than vice versa ($n = 5$ out of 24) ($p = 0.02$). The authors noted that not all patients whose treatment was classified as not successful opt to cross over. In the PROCESS study five SCS and 32 CMM patients requested crossover.

HRQoL outcomes

The PROCESS trial assessed HRQoL using Short Form 36 (SF-36; *Table 6*). At 6 months, the SCS group improved significantly in seven out of eight domains measured but not in the domain 'Role–emotional', whereas the control group only showed significant improvement in the domain 'General

TABLE 4 *Failed back surgery syndrome – medication outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis) NB different comparators	Opioid use, SCS group	Opioid use, control group	Comparison
PROCESS	6 months	50	44	Change from baseline $n = 28$ (56%)	Change from baseline $n = 31$ (70%)	OR 0.53 (99% CI 0.17 to 1.64) $p = 0.20$
North	Mean 2.9 years	23	26	Stable or decreased $n = 20$ (87%); increased $n = 3$ (13%)	Stable or decreased $n = 15$ (58%); increased $n = 11$ (42%)	$p = 0.025$

99% CI, 99% confidence intervals; OR, odds ratio.

TABLE 5 *Failed back surgery syndrome–functional outcomes measured by the Oswestry Disability Index (ODI)*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis) NB different comparators	ODI SCS group	ODI control group	ODI comparison
PROCESS	6 months	50	44	Mean 44.9 (SD 18.8) change from baseline $p < 0.001$	Mean 56.1 (SD 17.9) change from baseline $p = 0.85$	At 6 months, between-group risk difference –11.2 (99% CI –21.2 to –1.3) SCS group showed a significantly greater improvement in function compared with CMM patients ($p = 0.0002$).

99% CI, 99% confidence interval; SD, standard deviation.

health'. There was a significant difference between groups in seven out of eight domains $p \leq 0.02$, but not in 'Role–physical'.

Summary

Evidence from FBSS trials suggested that SCS was more successful than CMM or reoperation in terms of pain relief. SCS resulted in more reduction in use of opiates than reoperation. SCS was more effective than CMM in improving functional ability and HRQoL.

There was no difference between SCS and reoperation in pain related to daily activities or neurological function. Medication use was similar for SCS and CMM groups. Employment status was not improved by SCS, CMM or reoperation.

Clinical effectiveness in complex regional pain syndrome

One RCT (Kemler) included patients with CRPS type I and compared SCS plus physical therapy (PT) with PT alone. Details of the trial are presented in Appendix 5.2. The trial had adequate randomisation and allocation concealment and reported an ITT analysis.

Pain outcomes

The Kemler trial (*Table 7*) reported that the SCS group showed significantly more reduction in pain as measured by VAS than the PT group at 6 months ($p < 0.001$) and 2 years ($p = 0.001$) but not at 5 years ($p = 0.25$). The change in significance was partly the result of a lower pain reduction in the SCS group and partly of a reduction in pain in the PT group at longer follow-up.

The Kemler trial also measured Global Perceived Effect (GPE), a seven-point scale, finding thatsignificantly more SCS patients than PT patients considered that they were 'much improved' at 6 months ($p = 0.01$), and at 2 years ($p = 0.001$). This difference was also significant in a per treatment analysis at 6 months and 2 years ($p < 0.001$). A review by Grabow *et al.*[50] calculated the number needed to treat to obtain at least one patient with a GPE rating of 'much improved' as 3.0 (95% CI 1.9–7.0), which was comparable to that for medications for chronic pain.[50] When the Kemler trial measured 'success' as either 'much improved' on GPE or a 50% or more decrease in pain measured by VAS, 20 of 35 SCS patients achieved success at 2 years.[67]

Functional outcomes

Functional outcome was measured using the Jebsen test for hand function and a standardised test devised by the authors for foot function, testing speed to perform tasks (*Table 8*), strength and function (Appendix 5.2). There was no clinically important improvement in function in either of the treatment groups at 6 months or 2 years. Apart from ankle range of motion reaching borderline significance ($p = 0.04$) favouring the PT group at 2 years (based on $n = 5$ in control group), none of the function tests differed between groups at 6 months or 2 years.

HRQoL outcomes

The HRQoL outcome measures cited by Kemler were Nottingham Health Profile, EuroQol 5D, the short version of the Sickness Impact Profile and Self-rating Depression Scale. There were no differences in HRQoL between groups in any ITT analysis (*Table 9*). Per treatment analyses at

TABLE 6 *Failed back surgery syndrome – health-related quality of life outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)	SF-36 SCS group; mean (SD) change from baseline	SF-36 control group; mean (SD) change from baseline:	Comparison; difference in means (99% CI) significant difference for:
PROCESS	6 months	50	44	Physical function 38.1 (23.0) $p = 0.001$	Physical function 21.8 (16.2) $p = 0.67$	Physical function 16.3 (5.3–27.2) $p < 0.001$
				Role–physical 17.5 (32.4) $p = 0.006$	Role–physical 8.0 (22.7) $p = 0.67$	Role–physical 9.5 (–5.9 to 24.9) $p = 0.12$
				Bodily pain 33.0 (20.9) $p < 0.001$	Bodily pain 19.5 (12.9) $p = 0.12$	Bodily pain 13.4 (3.9–23.0) $p < 0.001$
				General health 52.8 (22.3) $p = 0.004$	General health 41.3 (24.4) $p = 0.007$	General health 11.5 (–1.2 to 24.1) $p < 0.001$
				Vitality 41.3 (21.5) $p = 0.002$	Vitality 31.1 (20.9) $p = 0.97$	Vitality 10.2 (–1.4 to 21.7) $p = 0.01$
				Social functioning 49.3 (29.7) $p = 0.001$	Social functioning 33.5 (18.4) $p = 0.65$	Social functioning 15.7 (2.1–29.4) $p = 0.002$
				Role–emotional 51.3 (44.3) $p = 0.09$	Role–emotional 29.5 (40.8) $p = 0.31$	Role–emotional 21.8 (–1.4 to 45.0) $p = 0.02$
				Mental health 62.6 (22.2) $p = 0.004$	Mental health 50.1 (23.3) $p = 0.16$	Mental health 12.5 (0.1 to 24.8) $p = 0.002$; non-significant between groups

99% CI, 99% confidence interval; SD, standard deviation.

6 months and 24 months suggested that the SCS group ($n = 24$) had significantly more improvement than the PT group as measured on the pain component of the Nottingham Health Profile, for patients with either an affected hand ($p = 0.02$) or an affected foot ($p = 0.008$).

Summary

Evidence from the CRPS trial suggests that SCS was more effective than PT in reducing pain at 6 months and 2 years, but not at 5 years, and was more successful in terms of patients' GPE of treatment.

SCS and PT were similar in effectiveness for functional ability of the affected hand or foot, and for HRQoL.

TABLE 7 *Complex regional pain syndrome – pain outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)	VAS change in pain from baseline (mean) SCS group	VAS change in pain from baseline (mean) Control group	Comparison
Kemler	6 months	36	18	Reduction of 2.4 cm	Increase of 0.2 cm	$p < 0.001$
Kemler	2 years	35	16	Reduction of 2.1 cm (SD 2.8)	No change 0 cm (SD 1.5)	$p = 0.001$
Kemler	5 years	31	13	Reduction of 1.7 cm	Reduction of 1.0 cm	$p = 0.25$

TABLE 8 *Complex regional pain syndrome – functional outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)	Functional ability SCS group (seconds required to perform task)	Functional ability control group (seconds required to perform task)	Comparison
Kemler	6 months	$n = 22$ for hand	$n = 11$ for hand	Hand function mean 2 s (SD 10)	Hand function mean –1 s (SD 5)	Hand function $p = 0.21$
		$n = 14$ for foot	$n = 6$ for foot	Foot function mean –1 s (SD 3)	Foot function mean –1 s (SD 3)	Foot function $p = 0.96$
Kemler	2 years	$n = 21$ for hand	$n = 10$ for hand	Hand function mean 2 s (SD 14)	Hand function mean 4 s (SD 21)	Hand function $p = 0.78$
		$n = 14$ for foot	$n = 5$ for foot	Foot function mean –3 s (SD 4)	Foot function mean –5 s (SD 5)	Foot function $p = 0.48$

Clinical effectiveness in ischaemic pain

Four RCTs were available for CLI (see Clinical effectiveness in critical limb ischaemia) and four RCTs were available for angina (see Clinical effectiveness in refractory angina). Only one of these (ESES) had pain relief as a primary outcome measure, with the other trials being designed to assess functional outcomes.

One systematic review also identified case series for ischaemic limb pain and angina. As previously stated (see Clinical effectiveness in neuropathic pain), case series are considered methodologically weak, but the review found that SCS was reported as having a favourable effect in the majority of case series for ischaemic limb pain and angina pain.[48]

Clinical effectiveness in critical limb ischaemia

Four CLI trials were included. Although trials did not explicitly state pain duration, they were included because stage of disease indicated a duration of at least 3 months. Populations of all four trials had inoperable CLI, there was some difference in proportions of patients with ulceration, and one trial (Suy) included Buerger's disease. There was some difference between trials in medications used in treatment and comparator groups (Appendix 5.3). All four trials presented an ITT analysis. ESES had adequate randomisation and allocation concealment, but these were unclear in the other three trials (Suy, Jivegard, Claeys). Baseline comparability was achieved for all trials, although not in the Claeys trial for previous vascular leg surgeries.

Pain outcomes

Two of the four included trials reported pain outcomes. The ESES trial (*Table 10*) measured pain on VAS at 1, 6, 12 and 18 months and found no difference between SCS and CMM groups. ESES also found that the pain-rating index of the McGill Pain Questionnaire showed that for both the SCS and CMM groups pain was decreased significantly at 1 month and 3 months ($p < 0.001$), remaining stable up to 18 months, with no difference between groups. In the Jivegard trial the SCS group had significant long-term pain relief throughout 18 months of follow-up ($p < 0.01$), and the analgesics group had significant pain relief at 2 months follow-up ($p < 0.05$), but no significant pain relief at 6 months or 12 months follow-up. Skin temperature in the ischaemic area, measured by

TABLE 9 *Complex regional pain syndrome – health-related quality of life outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)	HRQoL SCS group; change in HRQoL%	HRQoL control group; change in HRQoL%	Comparison
Kemler	6 months	36	18	Mean 6 (SD 22)	Mean 3 (SD 18)	$p = 0.58$
Kemler	2 years	35	16	Mean 7 (SD 20)	Mean 12 (SD 18)	$p = 0.41$

VAS, did not differ between the SCS and analgesics groups and neither group differed significantly from baseline (Jivegard).

When considering only non-amputated patients, ESES reported more pain relief in the SCS group than the CMM group, whereas in the case of amputation pain relief slightly favoured CMM.

Medication outcomes
The ESES found a reduction in the numbers of patients taking narcotics in both SCS and CMM groups (*Table 11*). In a different measure of medication use, ESES used a Medication Quantification Scale to evaluate the use of analgesics, and found a significant difference between groups at 1 month and 3 months ($p < 0.001$) and 6 months ($p = 0.002$), with SCS on a lower dose than CMM. This difference was borderline significant at 12 months ($p = 0.055$) and non-significant at 18 months ($p = 0.70$). The direct pain measurement outcomes of this trial showed no difference between groups, but the lower medication use in the SCS group up to 6 months may have affected the pain measures.

Functional outcomes
All four trials reported limb survival or amputation rates (*Table 12*), and none of the trials found a significant difference between SCS and control groups. The Jivegard trial reported a borderline significant difference between groups when categorising amputations by none/moderate/major, with fewer major amputations in the SCS than in the analgesics group.

Despite differences in trial comparators, two meta-analyses have been published. A meta-analysis by Klomp *et al*.[99] including the studies ESES, ESES pilot, Suy, Jivegard and Claeys, produced a non-significant relative risk of amputation at 18 months of 0.80 (95% CI 0.60 to 1.06) [risk difference –0.07 (95% CI –0.17 to 0.03) for SCS with reference to control]. The systematic review by Ubbink *et al*.[87] included a non-randomised trial (Amann[101]) in a meta-analysis of limb salvage at 12 months which indicated significantly greater limb salvage with SCS compared with control; however, by excluding the non-randomised trial a non-significant difference was found between SCS and control RR 0.78 (95% CI 0.58 to 1.04), risk difference 0.09 (95%CI –0.01 to 0.19).

The systolic toe to brachial pressure index did not differ between the SCS and analgesics groups in the Jivegard trial, with values for both groups significantly increased from baseline at 2 months but not at 6 months. Jivegard found no difference between SCS and analgesics groups in the ankle to brachial pressure index, with neither group differing from baseline. For the ankle to brachial pressure index Claeys found that the mean change for SCS patients was significantly different ($p < 0.02$) from the mean change for patients taking prostaglandin E1 at 12 months, although the mean ankle to brachial pressure index of the SCS patients was not significantly increased. Transcutaneous oxygen pressure ($TcPo_2$) did not differ between the SCS and CMM groups (ESES), but was higher ($p < 0.05$) in SCS patients than in the prostaglandin E1 group at 12 months.

A priori subgroup analysis of the ESES trial found that patients with intermediate skin microcirculation before treatment showed a non-significant trend for the SCS group to have a lower amputation rate at 18 months follow-up (Appendix 5.3). Success within subgroups can suggest that selection criteria be employed to decide which patients are more likely to benefit from SCS. Ubbink and Vermeulen[102] suggested that SCS may be more effective for CLI patients if they have a $TcPo_2$ between 10 and 30 mmHg. The systematic review by Ubbink *et al*.[87] included

TABLE 10 *Critical limb ischaemia – pain outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)	VAS change in pain from baseline (mean) SCS group	VAS change in pain from baseline (mean) Control group	Comparison
ESES	6 months	44	42	Reduction of 1.35 cm	Reduction of 2.57 cm	Non-significant
ESES	12 months	42	38	Reduction of 1.94 cm	Reduction of 2.15 cm	Non-significant
ESES	18 months	27	24	Reduction of 2.45 cm	Reduction of 2.61 cm	Non-significant

TABLE 11 *Critical limb ischaemia – medication outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis no. taking narcotics at baseline)	Number of participants in control group (in analysis no. taking narcotics at baseline)	Narcotic use SCS group (no. taking narcotics)	Narcotic use control group (no. taking narcotics)	Comparison
ESES	6 months	18	21	5	12	NR
ESES	12 months	18	21	4	6	NR
ESES	18 months	18	21	2	0	Non-significant $p = 0.70$

NR, not reported.

a non-randomised trial[101] that suggested patients with adequate $TcPo_2$, pain relief and paraesthesia coverage in response to test stimulation, benefited significantly more from SCS than from conventional treatment. Subgroup analysis for the Jivegard trial, in surviving patients without arterial hypertension, found a significantly lower ($p = 0.045$) amputation rate in the SCS group than the analgesics group. On a different outcome, the Claeys trial suggested a better response with SCS in patients with $TcPo_2 > 10$ mmHg in terms of ulcer healing.

HRQoL outcomes

One of the trials, ESES, assessed HRQoL (*Table 13*). There was no significant difference between SCS and CMM on Nottingham Health Profile (NHP; significant reduction in NHP pain score for both groups), EuroQol 5D, or the mobility index of the Sickness Impact Profile.

Subgroup analysis in ESES found that non-amputated patients had better mobility and energy scores on NHP in the SCS compared with the control group.

Summary

Evidence from CLI trials suggests that SCS was more effective than CMM in reducing the use of analgesics up to 6 months, but not at 18 months.

Although there was significant pain relief achieved, there was no significant difference between groups in terms of pain relief, for SCS versus CMM or analgesics treatment. SCS had similar limb survival rates to CMM, or analgesics treatment, or prostaglandin E1. SCS and CMM were similarly effective in improving HRQoL.

Clinical effectiveness in refractory angina

There were four trials of angina in coronary artery disease. The trials differed in populations, comparators and follow-up. In three of the trials participants were considered ineligible for coronary artery bypass grafting (CABG), whereas in one trial (ESBY) participants could undergo CABG, although they were expected to have no prognostic benefit from it. In three of the trials participants were ineligible for percutaneous myocardial revascularisation (PMR), whereas in one trial (SPiRiT) participants could undergo PMR, although they were considered unsuitable for conventional revascularisation. Populations were not typical of angina populations, but rather refractory angina, as trials included populations that either had refractory angina, meaning their coronary artery disease made them ineligible for conventional revascularisation (DeJongste, SPiRiT, Hautvast), or they were considered not to have improved prognosis from conventional revascularisation (ESBY).

One of the trials (SPiRiT) had adequate random assignment and allocation concealment, another trial (DeJongste) had adequate allocation concealment and unclear random assignment, whereas these were unclear for other trials (ESBY, Hautvast). Two trials did not report ITT analysis (ESBY, SPiRiT). The other two trials, which had only 6 or 6–8 weeks follow-up, did not report any drop-outs or losses to follow-up, and did present ITT analysis. Baseline comparability was achieved apart from in the ESBY trial for renal disease and smoking, and in the Hautvast trial for number of myocardial infarctions, and number of coronary angioplasties.

Pain outcomes

One of the trials (Hautvast) reported pain as measured by VAS (*Table 14*). There was no significant difference between SCS and inactive stimulator groups, despite the SCS group having a significant reduction in mean pain score at 6 weeks ($p = 0.03$).

TABLE 12 *Critical limb ischaemia – functional outcomes*

Trial	Follow-up	No. in SCS group (in analysis)	No. in control group (in analysis) NB different comparators	Amputation SCS group	Amputation control group	Limb survival SCS group	Limb survival control group	Comparison
ESES	6 months	60	60	Major amputation at 6 months $n = 19$	Major amputation at 6 months $n = 18$	66%	68%	Non-significant
ESES	12 months	60	60	24[88]	29[88]	60%	46%	Non-significant
ESES	24 months	60	60	Major amputation $n = 25$	Major amputation $n = 29$	52%	46%	Non-significant between groups $p = 0.47$, hazard ratio for SCS vs control group 0.81 (0.47–1.51)
ESES pilot	12 months	19	18			67%	47%	Non-significant $p = 0.082$ hazard ratio 2.3
ESES pilot	24 months	19	18			61%	39%	Non-significant $p = 0.08$
Suy	24 months	20	18	Major amputation $n = 6$	Major amputation $n = 9$			Survival with endpoints death without major amputation or major amputation, non-significant between groups $p = 0.42$
Jivegard	18 months	25	26	Nine amputations, of which one major amputation	14 amputations, of which six major amputations	62%	45%	Non-significant between groups in limb salvage rates. Comparison of none/moderate/major amputations $p = 0.05$
Claeys	12 months	45	41	Minor amputations $n = 6$ (13%); major amputations $n = 7$ (16%)	Minor amputations $n = 6$ (15%); major amputations $n = 8$ (20%)			Non-significant for minor and major amputations

TABLE 13 *Critical limb ischaemia – health-related quality of life outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)	NHP SCS group	NHP control group	Comparison
ESES	6 months	44	41	Overall NHP mean 35 (SE 2.6); from baseline overall NHP mean 48 (SE 2.6)	Overall NHP mean 34 (SE 3); from baseline overall NHP mean 47 (SE 2.6)	Overall NHP non-significant
ESES	18 months	27	24	Overall NHP mean 35 (SE 2.6); from baseline overall NHP mean 48 (SE2.6)	Overall NHP mean 34 (SE 3); from baseline overall NHP mean 47 (SE 2.6)	Overall NHP non-significant
				NHP Pain Score 31 (SE 6), significant reduction from baseline; baseline 70 ($n = 57$, SE 3.9)	NHP Pain Score 36 (SE 6), significant reduction from baseline; baseline 72 (SE 3.5)	NHP Pain Score non-significant between groups

SE, standard error.

Medication outcomes

Three trials (DeJongste, ESBY, Hautvast) investigated nitrate consumption and all found significant differences between SCS and the control group (*Table 15*). DeJongste found a greater reduction ($p < 0.05$) in glyceryl trinitrate consumption for SCS than for the No SCS group at 6–8 weeks. The ESBY trial found significantly more reduction for CABG, than for SCS group, for long-acting nitrates ($p < 0.0001$) at 6 months, although there was no significant difference in short-acting nitrates with both groups having a significant reduction ($p < 0.0001$) in consumption from baseline. Hautvast found a significant reduction ($p = 0.01$) in nitrate consumption in the SCS group at 6 weeks, which differed significantly from the Inactive stimulator group ($p = 0.03$).

Angina – functional outcomes

Three of the trials (DeJongste, ESBY, Hautvast) assessed the frequency of angina attacks (*Table 16*). There was a significantly reduced frequency of angina attacks in the SCS group compared with the No SCS group ($p < 0.05$) at 6–8 weeks (DeJongste), and the SCS compared with Inactive stimulator at 6 weeks ($p = 0.01$) (Hautvast). The ESBY trial found no difference between treatment groups, with a significant reduction in angina attacks for both the SCS and CABG groups at 6 months.

The SPiRiT trial assessed change in angina class as measured by the Canadian Cardiovascular Society angina scale. No difference was found at 12 months between the SCS and PMR groups in an analysis treating deaths and dropouts as failures, although an analysis excluding patients without follow-up indicated that the SCS group had greater improvement in the Canadian Cardiovascular Society class ($p = 0.042$).

Three of the trials had the SCS device switched on during exercise testing (DeJongste, SPiRiT, Hautvast). Total exercise duration (*Table 17*) was significantly more improved in the SCS than the No SCS group ($p < 0.03$) (DeJongste), and in SCS than in the Inactive stimulator ($p = 0.03$)

TABLE 14 *Angina – pain outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)	VAS change in pain from baseline (mean) SCS group	VAS change in pain from baseline (mean) Control group	Comparison
Hautvast	6 weeks	13	12	Reduction of 1.1 cm	Reduction of 0.2 cm	Non-significant

TABLE 15 *Angina – medication outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)[a]	Nitrate use SCS group	Nitrate use control group	Comparison
DeJongste	6–8 weeks	8	9	Median GTN per week 1.6 (0.3–6.9), significant reduction from baseline $p < 0.004$; baseline 13.3 (95% CI 8.8–17.7)	Median GTN per week median 8.5 (2.8–27.1) non-significant from baseline; baseline 8.3 (95% CI 3.3–32.6)	$p < 0.05$
ESBY	6 months	49	40	Nitrate consumption, doses/week baseline 15.2 (18.8) 6-month follow-up 4.1 (10.5) significant reduction from baseline $p < 0.0001$	Nitrate consumption, doses/week baseline 13.7 (12.1) 6-month follow-up 3.1 (8.7) significant reduction from baseline $p < 0.0001$	Non-significant between groups for consumption of short-acting nitrates. Significantly more reduction in control, than in SCS group, for long-acting nitrates $p < 0.0001$
Hautvast	6 weeks	13	12	Nitrogen consumption (tablets) 1.6 ± 2.2, significantly different from baseline, difference (%) -48 ± 49; $p = 0.01$ (baseline 3.6 ± 2.8)	Nitrogen consumption (tablets) 2.6 ± 1.7, non-significant from baseline difference (%) 27 ± 63 (baseline 2.3 ± 1.6)	$p = 0.03$

GTN, glyceryl trinitrate.
a Different comparators.

(Hautvast), but there was no difference between SCS and PMR (SPiRiT). Exercise testing of time to angina was significantly more improved in the SCS than the No SCS group ($p < 0.05$) (DeJongste), and in SCS than Inactive stimulator ($p = 0.01$) (Hautvast), and in SCS than PMR at 3 months ($p = 0.028$) although it was not significantly different at 12 months (SPiRiT).

In the ESBY trial, the SCS patients had the device switched off during exercise testing, which would be expected to diminish its effectiveness (ESBY authors had previously reported on a case series of angina patients in which SCS when switched on could improve exercise training[103]). The exercise test in the ESBY trial found that at 6 months CABG had a significantly greater increase in maximum workload capacity than SCS ($p = 0.02$).

HRQoL outcomes

All four trials evaluated HRQoL, all using different outcome measures. DeJongste assessed Daily activity and Social activity scores and showed a significantly greater improvement for both measures ($p < 0.05$) for SCS compared with the No SCS group at 6–8 weeks (*Table 18*). The ESBY trial found no differences between the CABG and SCS groups, at 6 months and 58 months, in any subcategory of NHP, with both groups significantly improving from baseline ($p < 0.001$). Both groups had significant improvements in 'energy' and 'pain' scores, and the magnitude of improvement in NHP total score for both groups was > 30%, with both groups reaching a level comparable to that of a healthy population. There was no difference between SCS and PMR as measured by the Short Form 36 at 3 and 12 months (SPiRiT). Hautvast found no difference between SCS and Inactive

TABLE 16 *Angina – functional outcomes; angina attacks/class*

Trial	Follow-up	No. in SCS group (in analysis)	No. in control group (in analysis)[a]	Frequency angina SCS group	Frequency angina control group	Comparison
DeJongste	6–8 weeks	8	9	Median angina pectoris per week 9.0 (4.0–14.2) significant improvement from baseline $p < 0.003$; baseline 16.6 (95% CI 11.4–26.1)	Median angina pectoris per week 13.6 (7.7–20.8) non-significant from baseline; baseline 16.5 (95% CI 9.0–23.9)	$p < 0.05$
ESBY	6 months	49	36	Angina attack frequency, attacks/week mean 4.4 (SD 7.4) significant reduction $p < 0.0001$; baseline mean 14.6 (SD 13.5)	Angina attack frequency, attacks/week mean 5.2 (SD 10.3) significant reduction $p < 0.0001$; baseline mean 16.2 (SD 12.6)	Non-significant
Hautvast	6 weeks	13	12	Angina attacks (per day) 2.3 ± 1.9, significant difference from baseline difference (%) –41 ± 44, $p = 0.01$; baseline 4.3 ± 2.4	Angina attacks (per day) 3.2 ± 1.5, difference from baseline (%) 33±82 (baseline 2.9±1.4)	$p = 0.01$

a Different comparators.

stimulator groups at 6 weeks when measured using the Linear Analogue Self-Assessment scale, although the SCS group showed a significant improvement ($p = 0.01$) (*Table 18*).

Two trials assessed disease-specific quality of life. The ESBY trial employed the Questionnaire Angina Pectoris QLQ-AP, and found no difference between SCS and CABG groups at 6 months and 58 months, with both groups showing significant improvements at 6 months ($p < 0.001$) and the results remaining consistent after 4.8 years. The SPiRiT trial found no difference between SCS and PMR groups on the Seattle Angina Questionnaire, with both groups improved at 3 and 12 months.

Summary

Evidence from Angina trials suggested that SCS was more effective than No SCS or Inactive stimulator for nitrate consumption, frequency of angina attacks, exercise duration and time to angina at 6–8 weeks. SCS was also more effective than PMR (at 3 months, not at 12 months) for time to angina. HRQoL was more improved by SCS than No SCS at 6–8 weeks.

There was no difference between SCS and Inactive stimulator in terms of pain relief. SCS and CABG had similar results for short-acting nitrates and frequency of angina attacks. There was no difference in effectiveness of SCS and PMR for change in angina class or exercise duration. SCS did not differ from CABG or PMR or Inactive stimulator in terms of HRQoL.

The SCS was less effective than CABG in reducing consumption of long-acting nitrates. SCS was less effective than CABG in increasing maximum workload capacity, although the SCS device was switched off during this comparison.

Complications and adverse events

Numbers of reported SCS device-related complications are shown in *Table 19*. SCS device-related complications included electrode migration,

TABLE 17 *Angina – functional outcomes; exercise tests*

Trial	Follow-up	No. in SCS group (in analysis)	No. in control group (in analysis)[a]	Exercise duration SCS group; mean ± SE	Exercise duration control group; mean ± SE	Exercise time to angina SCS group; mean ± SE	Exercise time to angina control group; mean ± SE	Comparison
DeJongste	6–8 weeks	8	9	Baseline 659± 121, 6–8 weeks 827 ± 138, change $p < 0.05$	Baseline 705 ± 136; 6–8 weeks 694 ± 67	Baseline 520 ± 138, 6–8 weeks 691 ± 174, change $p < 0.05$	Baseline 380 ± 78, 6–8 weeks 438 ± 91	Exercise duration $p < 0.03$ Time to angina $p < 0.05$
SPiRiT	3 months	32	33	7.33 (0.62)	7.32 ± 0.66	7.31 ± 0.73	6.26 ± 0.65	Exercise duration non-significant $p = 0.353$ Time to angina $p = 0.028$
SPiRiT	12 months	30	30	7.08 (0.67)	7.12 ± 0.71	7.31 ± 0.73	6.86 ± 0.82	Exercise duration non-significant $p = 0.466$; Time to angina non-significant $p = 0.191$
Hautvast	6 weeks	13	12	Baseline (seconds) 453 ± 156, 6 weeks 533 ± 184, difference (%) 19 ± 24 change $p = 0.03$	Baseline (seconds) 447 ± 214, 6 weeks 427 ± 177, difference (%) –0.2 ± 17	Baseline (seconds) 250 ± 67, 6 weeks 319 ± 85, difference (%) 39 ± 59; change $p = 0.03$	Baseline (seconds) 287 ± 119, 6 weeks 246 ± 97, difference (%) –9 ± 21	SCS group, compared with control, exercise duration was increased ($p = 0.03$), together with time to the onset of angina ($p = 0.01$)

a Different comparators.

lead fracture, loss of paraesthesia, dural puncture and infection (Appendix 5). The DeJongste trial had no complications during the study period, but during follow-up, when both groups had SCS, two (12%) patients had lead displacements requiring surgery.

Among the total of 403 implanted patients across all trials, four (1%) device removals were required, all as the result of infection. Across trials, the percentage of implantations requiring surgery to resolve a device-related complication, including device removals, ranged from 0% to 38% (5–38% if excluding two trials with under 2 months follow-up), which may be because of differences in follow-up periods, populations or clinical settings.

Some of the trials reported adverse events which were not related to the SCS device. These are reported in *Table 20*. Claeys reported adverse events from prostaglandin E1 but did not specify numbers of events according to treatment group. ESBY reported morbidity, and found no significant difference ($p = 0.08$) for total cardiac and cerebrovascular morbidity (including patients who had one or more event, fatal or non-fatal) between SCS ($n = 8$) and CABG ($n = 14$), although there were significantly ($p = 0.03$) more cerebrovascular events in the CABG group (eight events) than in the SCS group (two events).[80]

Discussion

Eleven prospective RCTs were included in the clinical effectiveness review. Evidence for the use of SCS in neuropathic pain was available from three RCTs. These trials were designed to assess pain relief. Evidence for the use of SCS in ischaemic pain was available from eight RCTs, only one (CLI trial) of these had a direct measure of pain as a primary outcome measure, with the emphasis of trials being on functional outcomes. Surgical, physical and pharmacological therapies used in comparators were all of relevance to current UK practice.

All three neuropathic pain trials reported pain outcomes. Trial data suggest that SCS is effective for pain relief in the neuropathic pain conditions

TABLE 18 *Angina – HRQoL outcomes*

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)[a]	HRQoL SCS group	HRQoL control group	Comparison
DeJongste	6–8 weeks	8	9	ADL score median 2.06 (95% CI 1.65–2.26) significant improved from baseline $p < 0.008$; baseline median 1.37 (95% CI 1.15–1.67). SAS median 2.10 (1.61–2.44) significant improvement from baseline $p < 0.005$; baseline 1.28 (95% CI 0.99–1.69)	ADL score median 1.25 (95% CI 1.10–1.71) non-significant from baseline; baseline median 1.24 (95% CI 1.06–1.50). SAS median 1.39 (1.10–1.65) non-significant from baseline; baseline 1.30 (95% CI 0.60–2.00)	ADL score significant difference between change in SCS group vs change in control group $p < 0.05$. SAS significant difference between change in SCS group vs change in control group $p < 0.05$.
Hautvast	6 weeks	13	12	LASA scale (cm) 6.8 ± 1.0, difference (%) 15 ± 19 significant difference from baseline $p = 0.01$ (baseline 6.0 ± 0.8)	LASA scale (cm) 6.2 ± 1.1, difference (%) 1 ± 15 non-significant from baseline (baseline 6.4 ± 1.7)	Non-significant

ADL, activities of daily living; LASA, linear analogue self-assessment; SAS, social activity score.
a Different comparators.

TABLE 19 *Spinal cord stimulation device-related complications*

Trial	Indication	Follow-up	Number of participants given SCS	Number of patients with device related event	Total device-related complications (some patients more than one event)	Surgery required to resolve	Removal of SCS required
PROCESS	FBSS	12 months	84	27	40	20 (24%)	
North	FBSS	6 months	17	4		4 (24%)	One removed and replaced (due to infection)
Kemler	CRPS	6 months	24	6	13 (11 + 2 dural puncture)	6 (5 + 1 removed) (28%)	One removed and replaced (due to infection)
Kemler	CRPS	24 months	24		76 (67 + 9 surgery)	9 (38%)	
ESES	CLI	18 months	57		25	12 (21%)	
Suy	CLI	24 months	20		3	3 (2 + 1 removed) (15%)	One removed and replaced (due to infection)
Jivegard	CLI	18 months	22	1	1	1 (5%)	
Claeys	CLI	12 months	45		3	3 (7%)	
DeJongste	Angina	6–8 weeks	8	0		(0%)	
ESBY	Angina	6 months	57			4 (3 + 1 removed) (7%)	One (due to infection)
SPiRiT	Angina	12 months	32		26	6 (19%)	
Hautvast	Angina	6 weeks	13	0		(0%)	

FBSS and CRPS type I. For FBSS, SCS was more successful than CMM or reoperation in terms of direct measures of pain relief. Medication use, which can indicate patients' experience of pain, was reduced to a greater extent in SCS than reoperation, although it was similar for the SCS and CMM groups. SCS was more effective than CMM in improving HRQoL. For FBSS, SCS was more effective than CMM in improving functional ability. There was no difference between SCS and reoperation in pain related to daily activities or neurological function. SCS did not differ from either CMM or reoperation in terms of employment status for FBSS. For CRPS, SCS was more effective than PT in reducing pain at 6 months and 2 years, but not at 5 years, and was more successful in terms of patients' GPE of treatment. SCS and PT were similar in effectiveness for HRQoL. Neither SCS nor PT significantly improved functional ability in CRPS.

The eight ischaemic condition trials reported functional outcome measures, but only two of the four CLI trials and one of the four angina trials reported direct outcome measures of pain, although the other angina trials reported nitrate use and frequency of angina attacks which could indicate pain experienced by patients. For CLI,

there was no significant difference between groups in terms of direct measures of pain relief, for SCS versus CMM or analgesic treatment. Analgesic use, which could indicate patients' experience of pain, was more reduced in SCS than CMM up to 6 months, but not at 18 months. SCS and CMM were similarly effective in improving HRQoL. SCS had similar limb survival rates to CMM, or analgesic treatment, or prostaglandin E1. For angina, nitrate consumption and frequency of angina attacks could indicate patients' experience of pain. SCS and CABG had similar results for short-acting nitrates and frequency of angina attacks. SCS was less effective than CABG in reducing consumption of long-acting nitrates. SCS did not differ from CABG or PMR in terms of HRQoL. Exercise testing showed similarities between SCS and PMR, and that SCS was less effective than CABG although this comparison was conducted with the SCS device switched off. In the two angina trials with follow-up of 6–8 weeks, and sample sizes of 25 or less, there was no difference between SCS and Inactive stimulator in terms of direct measurement of pain relief, although SCS was more effective than No SCS or Inactive stimulator for nitrate consumption and frequency of angina attacks. SCS did not differ from Inactive stimulator in terms of HRQoL. The HRQoL was more improved by SCS than by No SCS. Exercise testing suggested that SCS was more effective than No SCS or Inactive stimulator.

Complication rates varied across trials, but were usually minor. SCS device-related complications included electrode migration, lead fracture, loss of paraesthesia, dural puncture and infection. Across trials, the percentage of implantations requiring surgery to resolve a device-related complication, including device removals, ranged from 0% to 38%. Among the total of 403 implanted patients across all trials, there were four (1%) device removals required, all as the result of infection.

Although test stimulation was employed in all the neuropathic pain trials included in the review, it is unlikely that this would skew the results in favour of SCS because the FBSS trial with CMM comparator and the CRPS trial reported ITT analyses. These analyses included patients who did not receive permanent implants, and in the case of the FBSS trial patients failing test stimulation but receiving a permanent implant, analysed in their allocated SCS group.

The main limitation of the included trials was that they had small sample sizes. A power calculation was reported in six of the trials, most of which just achieved the recruitment target, and two of these were later found to be underpowered. There were trials adequately powered for primary outcome for FBSS, CRPS and one angina trial (with comparator PMR). Trials may not have been adequately powered to detect statistical or clinically meaningful differences in outcome measures.

It is possible that some definitions of success in terms of pain relief employed by trials were more stringent than improvements that patients would consider meaningful in improving pain. It should be noted that trial participants had received therapies other than SCS before trial participation and that these therapies had been unsuccessful.

Unclear randomisation and allocation concealment, and exclusion of participants from analysis are associated with overestimation of treatment effect. One FBSS trial, the CRPS trial, and one CLI trial had adequate methods of randomisation, allocation concealment and reported ITT analysis. The other FBSS trial had adequate methods of randomisation, but allocation concealment was unclear and not all randomised participants were included in the analyses. Of the CLI trials, all four presented ITT analysis, but only one had adequate randomisation and allocation concealment. Of the four angina trials, only one had adequate randomisation, one had adequate allocation concealment, and two presented ITT analysis whereas the other two excluded participants from analysis.

None of the trials were blinded. Blinding of patients and clinicians would have been impossible or unethical. Trials had no surgery, or different surgery, in the control group, or had an inactive stimulator of which patients would be aware because of lack of paraesthesia. For most of the outcome measures, patients themselves were the outcome assessors, which precluded the opportunity for employing independent blinded outcome assessors.

Trial data suggest that SCS is effective for the relief of neuropathic pain in FBSS and CRPS. There may be additional benefits of SCS for HRQoL and functional ability in FBSS. SCS was not shown to be more effective than other therapies in CLI apart from lower use of analgesics with SCS than CMM up to 6 months, although this did not continue at longer follow-up. There may be a subset of CLI patients that benefit from SCS, this requires further investigation. SCS appears to be effective at reducing some angina symptoms, at

TABLE 20 *Adverse events (non-SCS device-related)*

Trial	Indication	Follow-up	No. given SCS	No. given control treatment[a]	Adverse events SCS group (non-device related)	Adverse events control group
PROCESS	FBSS	12 months	84	44	Number of patients experiencing one or more non-device-related events 18 (35%).	Number of patients experiencing one or more non-device related event 25 (52%).
					Patients with one or more drug adverse events 2 (4%)	Patients with one or more drug adverse events 10 (21%)
					Drug adverse events 2	Drug adverse events 12
					Patients with one or more events of extra pain 0 (0%)	Patients with one or more events of extra pain 2 (4%)
					Events of extra pain 0	Events of extra pain 2
					Patients with one or more new illness/injury/conditions 13 (25%)	Patients with one or more new illness/injury/conditions 11 (23%)
					Events of new illness/injury/condition 16	Events of new illness/injury/condition 13
					Patients with one or more worsenings of pre-existing condition 7 (13%)	Patients with one or more worsening of pre-existing condition 7 (15%)
					Events of worsening of pre-existing condition 7	Events of worsening of pre-existing condition 10
ESES	CLI	18 months	59	60	Side effects occurred in four patients: duodenal perforation (1), nausea (2), pruritus (1).	Side effects were reported in 10 patients: upper gastrointestinal bleeding (3), nausea (7), dizziness (2)
SPiRiT	Angina	12 months	32	33	30 events	23 events in the control group were categorised as unrelated to the procedure. An additional four events were related to the PMR procedure

a Different comparators.

least short-term. Patients eligible for CABG may receive more benefit from CABG, although the side effect profile and morbidity indicate that SCS could be a safe alternative for patients considered high risk for CABG. Larger trials could clarify this apparent benefit of SCS for angina patients. It is unclear if the results could be generalised to other conditions. Non-RCT data suggest that SCS could be effective in other forms of neuropathic pain, and it may be effective in a subgroup of patients with CLI identified after publication of included trials, but this evidence is from studies of weaker methodology than RCTs, and so definitive conclusions are not drawn.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing economic literature

The primary objective of this review is to systematically identify and evaluate studies exploring the cost-effectiveness of SCS in the treatment of chronic neuropathic or ischaemic pain in the UK. The secondary objective is to evaluate methodologies used to inform our own economic evaluation.

Search strategy

Studies were identified through searches of MEDLINE (1996–present), EMBASE (from 1996), Cochrane Database of Systematic Reviews (CDSR), and the National Health Service (NHS) Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA). All searches were undertaken between August and September 2007. A list of the keyword strategies and the sources consulted are given in Appendix 2.

Inclusion and exclusion strategy

The titles and abstracts of papers identified through the searches outlined above were assessed for inclusion using the following criteria:

Inclusion criteria

- cost-effectiveness analyses – as opposed to cost–benefit or cost minimisation
- UK setting
- SCS as one of the studied alternatives (possibly combined with other interventions such as usual treatment)
- benefits estimated in terms of cost per life-years saved or cost per quality-adjusted life-year (QALY)
- adult populations
- study published in English.

Exclusion criteria

- studies that adapted published evaluations for other settings
- studies that do not report results in terms of incremental cost-effectiveness ratios.

Reviews discussing cost-effectiveness studies of SCS treatment were not included in this review but were retained for use in discussion. Non UK cost-effectiveness studies were retained and used to inform on possible modelling methodologies.

Quality assessment strategy

The quality of studies was assessed using a combination of key components of the *British Medical Journal* checklist for economic evaluations[104] together with the Eddy checklist on mathematical models employed in technology assessments.[105]

Results of review

Quantity and quality of research available

Electronic literature searches identified 36 potentially relevant publications. The inclusion and exclusion criteria were applied using the titles, abstracts and when available on-line, full papers. Of these, 27 studies did not meet the inclusion criteria based on titles and abstracts alone. Three UK studies were identified at this stage. More detailed evaluations revealed that two of the potential UK studies did not estimate benefits in terms of life-years saved or QALYs and therefore failed the inclusion criteria. These two UK studies reported physical functioning, drug use and work status and hence were retained for information. Only one UK study satisfied all the inclusion and exclusion criteria (*Figure 2*). No other studies were found that could inform the modelling process.

To compare the results, the currencies are converted to British pounds using the Gross Domestic Product Purchasing Power Parities,[106] and results are adjusted to 2007 using the Pay and Prices annual percentage increase.[107]

Published cost-effectiveness analysis

The study by Taylor and Taylor[108] evaluated the cost-effectiveness of SCS compared to conventional non-surgical treatment in patients with FBSS. A European health-care perspective was adopted, all costs were adjusted to 2003 price levels, and the results were calculated and reported as incremental cost per QALY ratios. Costs were discounted at

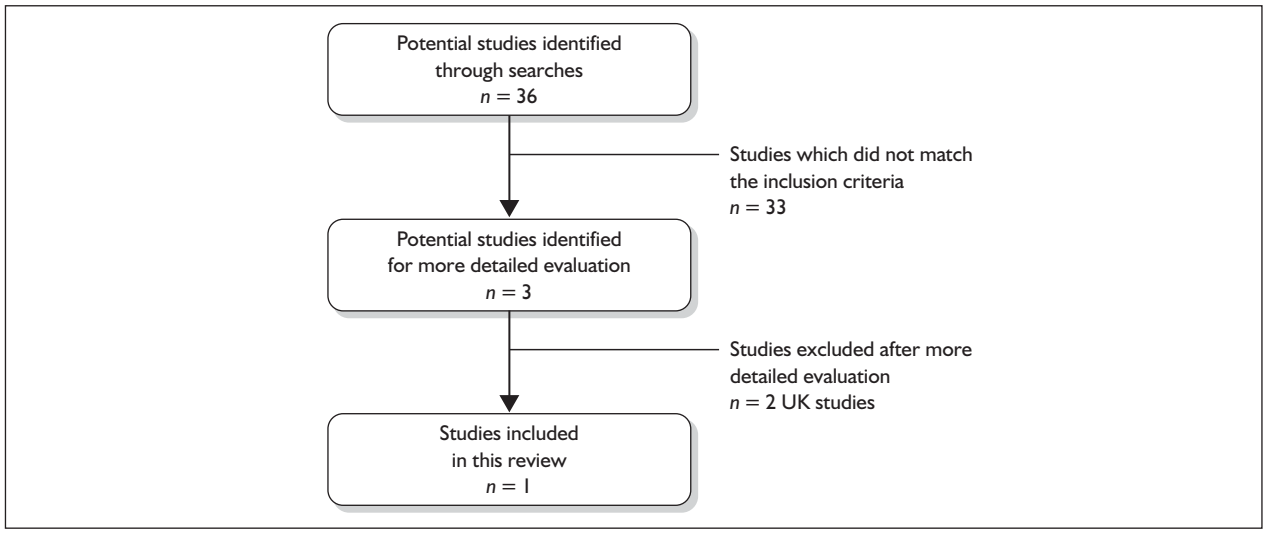

FIGURE 2 *Studies eliminated/selected for the review after applying inclusion/exclusion criteria.*

6% and benefits at 1.5%, according to National Institute for Clinical Excellence (NICE) guidance at that time.[109]

The model had two stages, a decision tree and a Markov model. The decision tree examined the costs and outcomes of SCS and conventional medical management (CMM) at 2 years. The Markov model extended the decision tree and was used to determine costs and outcomes over the lifetime of the patient. Patients entering SCS, in the decision tree, should undergo a screening period to assess their achieved pain relief. Those patients who achieved satisfactory pain relief had an SCS implant whereas the patients who failed were administered CMM.

As the costs associated with SCS and CMM in patients with FBSS were derived from a single Canadian centre, a European clinical reference panel was used to verify if the health-care resource utilisation of the Canadian study was reflective of a European setting. Canadian dollars (at 2000 prices) were converted to Euros (at 2003 prices) using inflation rates and purchasing parity power.

The incremental cost-effectiveness ratios (ICER) for SCS base case at 2 years were £33,053 per QALY. The short-term (2-year analysis) cost-effectiveness ratios ranged from £21,908 to £45,816 per QALY. In the lifetime analysis, it was found that SCS was dominant (it cost less and accrued more benefits) in both base case and one-way sensitivity analyses.

Review of the manufacturers' economic evaluation

A model was submitted by the Association of British Healthcare Industries (ABHI) on behalf of the following manufacturers: Advanced Neuromodulation Systems (St Jude Medical Ltd.), Boston Scientific Ltd and Medtronic Ltd. This model was designed to explore the cost-effectiveness of SCS in the management of chronic pain of neuropathic origin. The primary objective of the model was the economic evaluation of SCS for patients with FBSS and CRPS. These are the two primary indications for which SCS is currently used in England and Wales.

The following section describes the methods, the inputs and the results generated by the model. This is followed by a critique of the model and the implications of the findings.

Overview of the model submitted by ABHI

The model is defined as a two-stage model that uses a decision-analytical model for the short-term treatment (first 6 months) and a Markov process from 6 months and up to 15 years. Six mutually exclusive health states are defined: optimal pain relief with no complications, optimal pain relief with complications, suboptimal pain relief with no complications, suboptimal pain relief with complications, no perceived pain relief and death

from all causes of mortality (more details in Appendix 7).

Probabilities of events are based on three 6-month RCTs that examining SCS in the treatment of FBSS ($n = 60$, $n = 100$) and CRPS ($n = 54$).[59,62,65] The treatment success is defined as having a pain reduction of at least 50%. It is assumed that after the first six months the patients will remain in their present health states and will enter the Markov process. A three-month cycle is used and a probability of having complications is introduced. It is assumed that the complication is resolved within a cycle. Costs and benefits are discounted at 3.5%, as per current NICE guidelines.[110]

Populations considered in the model

The following three population groups are used:

Failed back surgery syndrome:

- patients suffering from persistent or recurrent neuropathic pain of radicular origin after lumbosacral spine surgery
- patients suffering a pain intensity of at least 50 mm on visual analogue scale (VAS; 0 = no pain, 100 = worst possible pain) for at least 6 months after having surgery.[59]

Failed back surgery syndrome:

- patients suffering from persistent or recurrent neuropathic pain of radicular origin after one or more lumbosacral spine surgeries that meet spinal surgical intervention criteria (these criteria are: pain refractory to conservative care, with concordant neurological tension and/or mechanical signs and imaging findings of neural compression).[62]

Complex regional pain syndrome:

- patients who met the diagnostic criteria for reflex sympathetic dystrophy established by the International Association for the Study of Pain, with impaired function and symptoms beyond the trauma,[65] patients suffering from a pain syndrome that affects one foot or one hand and which affects the entire foot or hand
- patients suffering the disease for at least 6 months and who do not have a sustained response to conventional pain medication, physical therapy, sympathetic blockade and transcutaneous electrical stimulation of nerves
- patients suffering pain intensity of at least 50 mm on a VAS from 0 mm (no pain) to 100 mm (very severe pain).

Comparators used in the model

SCS is used in conjunction with CMM, according to clinical practice.

Comparator 1: conventional medical management

The CMM comprises drug therapy and non-drug therapy. The drug therapy consists of opioids, non-steroidal anti-inflammatory drugs (NSAIDS), antidepressants and antiepileptics. On the other hand, non-drug therapy comprises physical rehabilitation, psychological rehabilitation, acupuncture, blocks, massage, chiropractic sessions, acupressure, etc.

Comparator 2: reoperation

Reoperation is defined as lumbosacral spine surgery. Reoperation patients also receive CMM.

Clinical parameters

Costs of health states, monitoring and treatments in the model

The costs of CMM are taken from the PROCESS study,[59] which reported data based on a follow-up of 6 months (*Table 21*). It is assumed that the annual cost of CMM in year 2 is reduced by 13.5% compared to the cost of year 1. This assumption was taken from a 5-year analysis of cost for CMM in Canada.[111]

Patients that undergo SCS have costs additional to CMM including screening, device implant, device reimplant, etc. (*Table 22*).

For FBSS patients that undergo revisional spinal surgery, it is assumed that the cost of CMM is the same as for SCS patients if they achieve optimal pain reduction. For those patients that do not achieve optimal pain reduction, it is assumed that the CMM cost is the same as for the patients that undergo CMM alone. The cost of revisional surgery of £4252 is taken from the NHS National Tariff R09.[112]

For CRPS patients, it is assumed that the costs of drug and non-drug treatments are similar to those for FBSS.

Utilities used in the model

As per NICE recommendations,[110] the health-state quality of life utilities are based on the EuroQol 5D (EQ-5D) administered within the PROCESS trial.[59]

TABLE 21 *Costs of drug and non-drug treatments for SCS + CMM and CMM alone*

	SCS + CMM (cost per patient)	CMM only (cost per patient)
Drug treatment in year 1	£3384[a]	£5328[a]
Average cost of non-drug treatment in year 1	£56[a]	£1608[a]
Average cost of CMM in year 1	£3440	£6936
Average cost of CMM (years 2 to 15)	£3440	£6000[b]

a PROCESS study.[59]
b £6936 × (1 – 0.135) = £6000.

TABLE 22 *Additional costs for patients who undergo SCS*

Average cost per screen	£4069	
Average cost of device implant	£11,269	
Average cost of failed screening	£1800	
Average cost of device explant	£1800	
Average cost of reimplant	£11,190	
	Initial implant	***Reimplant***
Cost of adverse events over 6 months	£622	£530
Adverse events (subsequent cycles)	£95	£95

TABLE 23 *Health-state utility values used in the model*

Health state	Utility value
Optimal pain relief	0.598
Optimal pain relief + complications	0.528
Suboptimal pain relief	0.258
Suboptimal pain relief + complications	0.258
No perceived pain reduction	0.168

The baseline utility value for all patients is 0.168 (*Table 23*).

Cost-effectiveness results estimated by the ABHI model

The results are summarised in *Table 24* and are presented in terms of cost per QALY (ICER). Over a 15-year time horizon and device longevity of 4 years (base case) and with 50% threshold criteria, the ICERs for FBSS and CRPS range from £7954 per QALY (for FBSS:SCS + CMM versus Reoperation) to £18,881 per QALY (for CRPS:SCS + CMM versus CMM).

Table 25 summarises the results using a 30% pain threshold criteria. It can be seen that the ICERs for FBSS and CRPS are increased and range from £17,463 per QALY (for FBSS:SCS + CMM versus reoperation) to £36,393 per QALY (for CRPS:SCS + CMM versus CMM).

Probabilistic results from the ABHI model

FBSS: SCS + CMM versus CMM

The results of the probabilistic analysis using a 15-year horizon suggest that SCS + CMM compared

TABLE 24 *Summary of results from the ABHI model*

50% pain threshold criteria	Cost difference	QALYs difference	ICER
FBSS: SCS + CMM vs CMM alone			
Base case: 4-year device longevity	£11,439	1.25	£9155
2-year device longevity			£30,285
7-year device longevity			£2745
Device longevity > 7 years			SCS + CMM dominates
FBSS: SCS + CMM vs reoperation			
Base case: 4-year device longevity	£10,651	1.34	£7954
2-year device longevity			£26,445
7-year device longevity			£2362
Device longevity > 7 years			SCS + CMM dominates
CRPS: SCS + CMM vs CMM alone			
Base case: 4-year device longevity	£12,041	0.64	£18,881
3-year device longevity			£28,015
10-year device longevity			£1607
Device longevity > 7 years			SCS + CMM dominates

TABLE 25 *Summary of results from the ABHI model for alternative scenario analyses*

30% pain threshold criteria	Cost difference	QALYs difference	ICER
FBSS: SCS + CMM vs CMM alone			
Base case: 4-year device longevity	£11,621	1.06	£10,962
2-year device longevity			£35,921
7-year device longevity			£3405
Device longevity > 7 years			SCS + CMM dominates
Maximum failure rate per annum on base case	£10,126	0.58	£17,463
FBSS: SCS + CMM vs reoperation			
Maximum failure rate per annum on base case	£9121	0.62	£14,726
CRPS: SCS + CMM vs CMM alone			
Maximum failure rate per annum on base case	£10,734	0.29	£36,393

to CMM alone produce more QALYs. The cost-effectiveness acceptability curve (ABHI report; Appendix 12 p.117) shows that when using a threshold of £20,000 per QALY the probability of SCS + CMM being cost-effective is around 80%. Additionally, at a £30,000 per QALY threshold, this probability is over 95%.

FBSS: SCS + CMM versus reoperation

The results found in the probabilistic analysis using a 15-year horizon suggest that SCS + CMM compared to reoperation produce more QALYs. The cost-effectiveness acceptability curve (ABHI report; Appendix 13 p.121) shows that when using a threshold of £20,000 per QALY the probability

of SCS + CMM being cost-effective is higher than 90%. Additionally, at a £30,000 per QALY threshold, this probability is around 98%.

CRPS: SCS + CMM versus CMM alone
Using a threshold of £20,000 per QALY, the results of the probabilistic analysis using a 15-year horizon suggest that the probability of SCS + CMM being cost-effective is over 40% whereas the probability at a £30,000 per QALY threshold is higher than 60% (ABHI report; Appendix 14 p.124).

Critique of the ABHI model

A full review of the model was given in the preceding sections. The quality of model was assessed using a combination of key components of the *British Medical Journal* checklist for economic evaluations[104] together with the Eddy checklist for mathematical models employed in technology assessments and presented in Appendix 6.[105] The model structure is suitable and is based on the Taylor and Taylor economic model.[108] The model is evidence-based and appropriate to answer the research question. The results are presented in incremental cost-effectiveness ratios and sensitivity analyses; additional probabilistic sensitivity analysis were performed.

Independent economic assessment by ScHARR

Objective

An independent economic assessment was performed by the School of Health and Related Research (ScHARR) at The University of Sheffield. The primary objective of this evaluation was to appraise the cost-effectiveness of the use of spinal cord stimulation in patients with neuropathic or ischaemic pain.

Methods

Neuropathic pain

A two-stage model was developed to explore the cost and health outcomes associated with a 15-year time period of treatment using a UK NHS perspective. A decision tree was used to model the first 6 months of treatment. The decision tree model was extended by a Markov model used to determine the cost and health outcomes over a 15-year time horizon. This time horizon was taken from the observational study conducted by Kumar *et al.*[113] that presents a Kaplan–Meier survival curve that illustrates subsequent gradual loss of pain control during a 15-year period. Taylor and Taylor first used this model structure to evaluate the cost-effectiveness of SCS compared to CMM.[108] Published RCT data are used to determine the treatments' efficacy for the first 6 months, thereafter effectiveness is extrapolated based on assumptions and observational data. The results are presented in terms of ICERs.

Population considered in the ScHARR economic evaluation
The model evaluates the cost-effectiveness of treatment in the three following populations:

- Adult patients (> 18 years old) with FBSS suffering from neuropathic pain of radicular origin predominantly in the legs for at least 6 months after one or more surgeries for a herniated disc (anatomically successful), as per the PROCESS trial[59] (SCS versus CMM). Their pain intensity is at least 50 mm on VAS (where 0 mm represents no pain and 100 mm represents the worst pain possible). Some patients had undergone other procedures, for instance spinal fusion, laminectomies or repeat lumbar disc operations.
- Adult patients (> 18 years old) with FBSS suffering from persistent or recurrent radicular pain, after one or more lumbosacral spine surgeries. All patients meet the criteria for surgical intervention (pain refractory to conservative care, with concordant neurological tension, and imaging finding of neural compression). Patients receive a second opinion from a neurosurgeon. Patients are excluded if they have a disabling neurological deficit in the distribution of a nerve root caused by surgically remediable compression or critical cauda equina compression. This patient population represents that of the North trial[62] (SCS versus reoperation).
- Patients with CRPS are based on the Kemler trial[65] (SCS versus CMM). Patients are adults (> 18 years old) who have suffered the indication for at least 6 months with impaired function and symptoms beyond the area of trauma. The patients' pain is restricted to one hand or foot and affects the entire hand or foot. Patients have not had a good level of response to standard treatment and have a pain intensity of at least 50 mm on a VAS (where 0 mm represents no pain and 100 mm represents very severe pain). Patients are excluded if they suffer from Raynaud's disease, neurological abnormalities not related to CRPS, other conditions affecting the function

of the qualifying extremity, a blood-clotting disorder or use of a pacemaker.

Treatment/comparator
Guidelines from the European Federation of Neurological Societies (EFNS) make an evidence-based recommendation for the use of SCS in the treatment of FBSS and CRPS type I.[21] The British Pain Society suggests that SCS may be considered when first-line therapies for chronic pain have failed. These therapies can include drug therapies, physical therapies (non-drug therapies) and surgical interventions.[35]

Comparator 1: conventional medical management
The CMM comprises drug therapy and non-drug therapy. The drug therapy basically consists of opioids, NSAIDS, antidepressants and antiepileptics. Non-drug therapy comprises physical rehabilitation, psychological rehabilitation, acupuncture, blocks, massage, chiropractic sessions, acupressure, etc.

Comparator 2: reoperation
Reoperation is defined as lumbosacral spine surgery. Reoperation patients also receive CMM.

Structure of the model
A decision tree model is used to explore the clinical pathway of individuals FBSS or CRPS in the short term. A Markov model is used to explore the clinical pathway of individuals suffering from FBSS or CRPS in the long term. The pathway is divided into a finite number of mutually exclusive health states. The proportion of patients in each health state is determined by the probabilities of achieving different levels of pain relief.

Time horizon
The model explores the costs and benefits accrued through pain relief over a 15-year period. This timeframe is taken from an observational clinical study that assesses clinical predictors of outcomes (e.g. age, sex, aetiology of pain, duration of pain, duration of treatment, employment status and quality of life) in patients who received SCS for the treatment of chronic pain. The study presents a Kaplan–Meier survival curve that illustrates subsequent gradual loss of pain control during a 15-year period. It was decided not to extrapolate beyond the 15-year period because of the increased uncertainty this would cause.[113]

Decision tree health states modelled
The first stage of the model (first 6 months) is defined with four possible health states:

- optimal pain relief with no complications
- optimal pain relief with complications
- suboptimal pain relief with no complications
- suboptimal pain relief with complications.

It is assumed that the patients do not change therapy during the first 6 months of treatment. The decision tree is populated with data from the Kumar *et al.* (PROCESS), North *et al.* and Kemler *et al.* RCTs and it replicates their randomisation phase, where the proportions of patients experiencing 'no pain relief' were not reported.[59,62,65] For the decision tree model all patients commence suffering from FBSS or CRPS and enter either the SCS trial or CMM (*Figures 3 and 4*).

Markov health states modelled
The second stage of the model (Markov process) is defined according to the indication. For FBSS, there are five possible health states:

- optimal pain relief (includes patients with or without complications)
- suboptimal pain relief (includes patients with or without complications)
- no pain relief (SCS)
- no pain relief (surgery)
- dead (all causes).

In this model, patients that have no pain relief would change treatment: patients on SCS will move to CMM and patients on CMM will undergo surgery (*Figure 5*). For CRPS, there are four possible health states:

- optimal pain relief (includes patients with or without complications)
- suboptimal pain relief (includes patients with or without complications)
- no pain relief (SCS)
- dead (all causes).

Surgery is not an option for CRPS patients (*Figure 6*). It is assumed that all patients are in the same health state that they were at the time of the decision tree when entering the Markov model. During each 3-month cycle of the model a proportion enter one of the health states defined in *Figure 5* and *Figure 6*.

Optimal pain relief is defined as having at least 50% pain reduction from baseline, measured on a VAS. Suboptimal pain relief is defined as having less than 50% pain reduction from baseline, measured on a VAS.

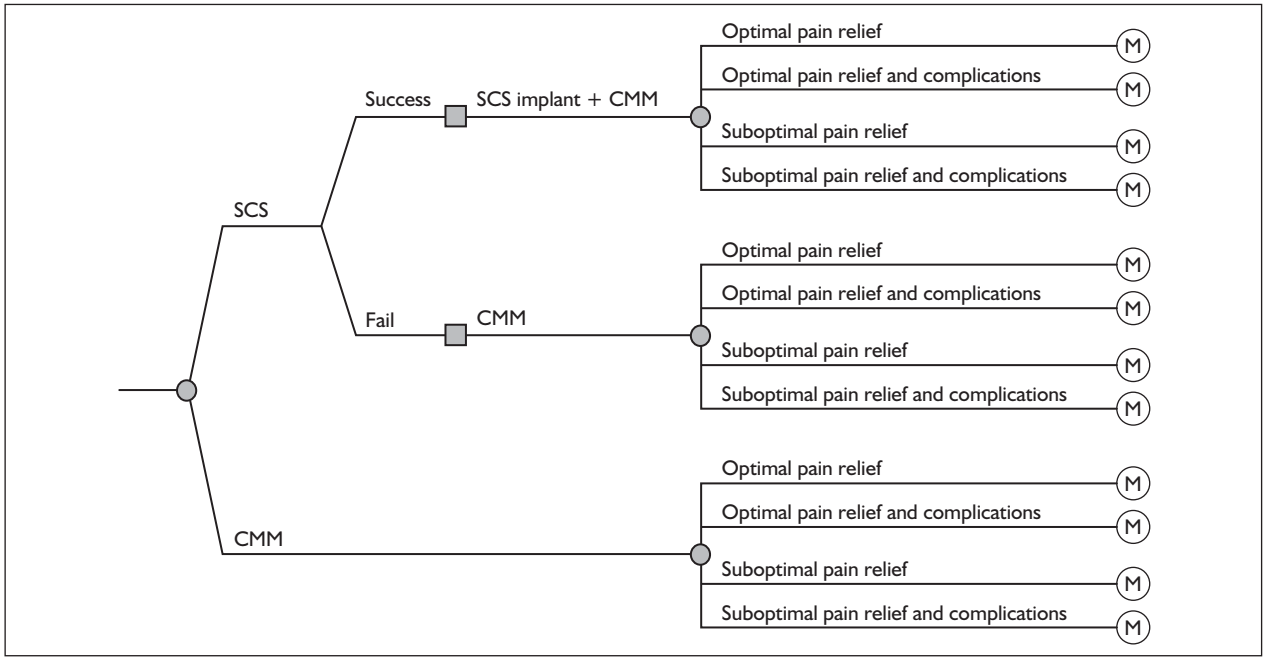

FIGURE 3 *Six-month decision tree for SCS + CMM versus CMM in FBSS and CRPS.*

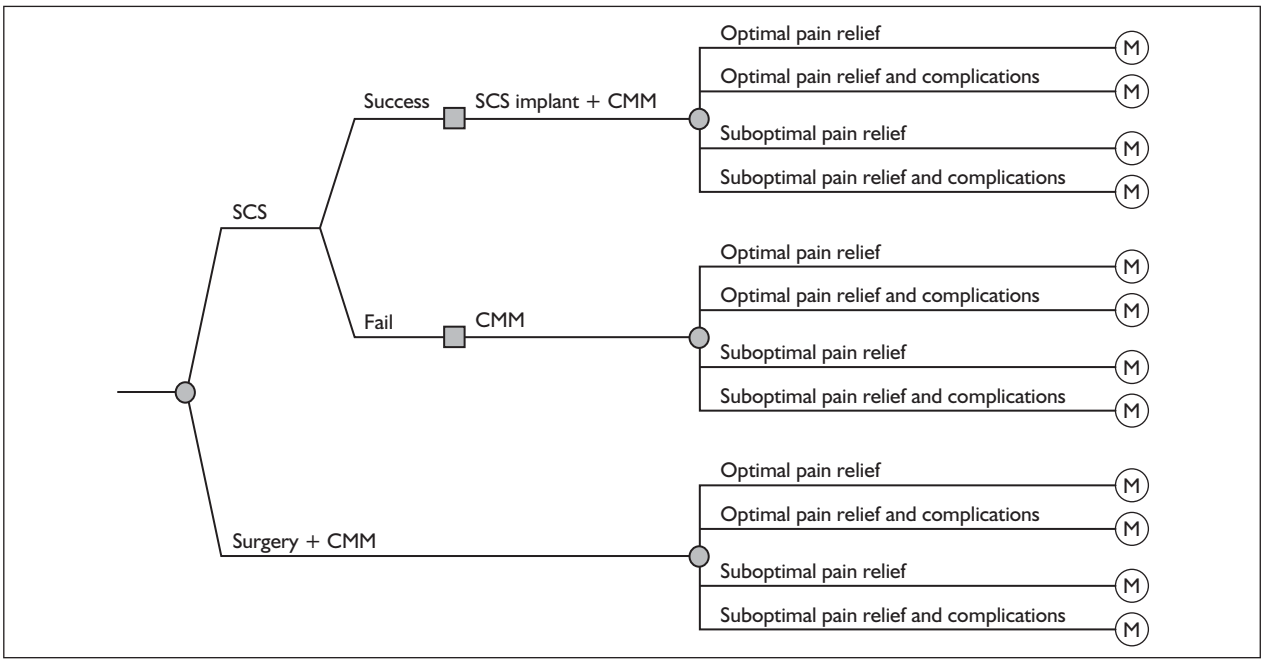

FIGURE 4 *Six-month decision tree for SCS + CMM versus reoperation in FBSS.*

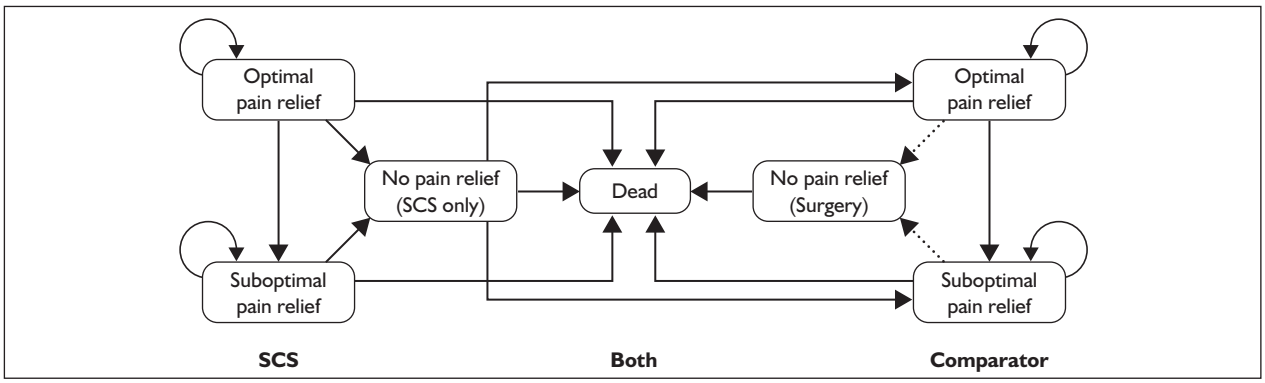

FIGURE 5 *Schematic of the long-term Markov model for FBSS.*

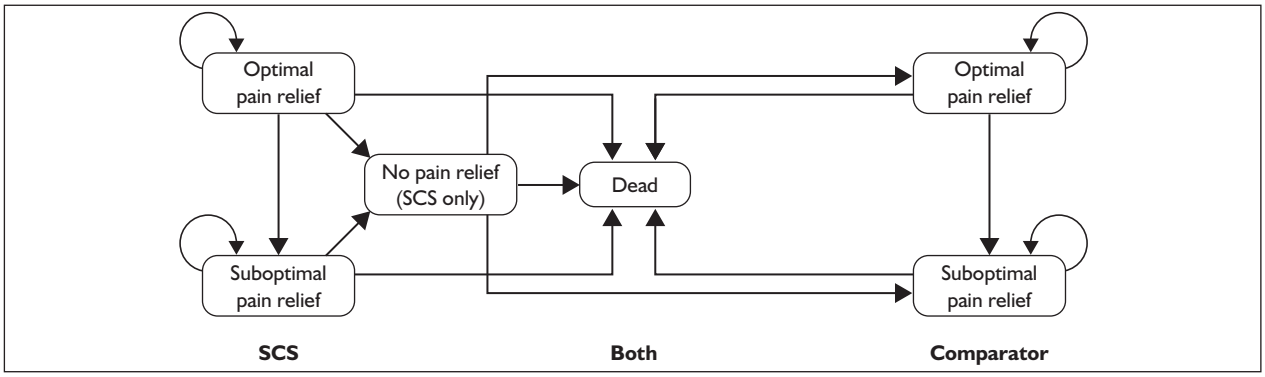

FIGURE 6 *Schematic of the long-term Markov model for CRPS.*

Perspective

A UK NHS perspective is used, therefore productivity lost through illness or costs incurred directly by patients are not included. Discount rates of 3.5% are applied to both costs and health benefits, according to current NICE guidelines.[110] Costs are at 2007 prices.

Probabilities of levels of pain relief

Short-term model

The probabilities of events for the 6-month models for FBSS and CRPS are presented in *Table 26*. These probabilities are derived from evidence included in the systematic review of clinical effectiveness presented in Chapter 3. The estimates of trial stimulation success and the number of patients that achieved pain relief of at least 50% were derived from the following RCTs:

- for FBSS: SCS + CMM versus CMM, the PROCESS trial[59]
- for FBSS: SCS + CMM versus reoperation, the North trial[62]
- CRPS: SCS + CMM versus CMM, the Kemler trial.[65]

In the FBSS: SCS + CMM versus CMM case, although the PROCESS trial[59] reported intention-to-treat analysis, five patients who failed the SCS trial stimulation still received an implant. In this health economic model, these patients were assumed to undergo CMM. Therefore, after SCS trial stimulation a total of nine patients received CMM.

The Kemler trial does not report the number of patients that achieved pain relief of at least 50%, the 44.4% presented in *Table 26* is an assumption taken from the ABHI report.[65] The underlying

parameter uncertainty is taken into account by sensitivity analyses performed in this report.

Long-term model

According to the 22-year follow-up SCS study conducted by Kumar *et al*.,[113] complications were the result of fractured electrodes, displaced electrodes, hardware malfunctions, biological factors or infections. Taylor *et al*.[49] conducted a systematic review for chronic back and leg pain and FBSS. In this review, they reported that an overall 43% of patients with implanted SCS experienced one or more complications, of these complications 27% were the result of electrode or lead problems, 6% infections and 10% extension cable problems.[49] This gives a rate of 18% of patients with SCS experiencing complications. Therefore, it is assumed that the annual rate of complications after the first 6 months is 18%.

A Swedish RCT of treatment of chronic low back pain with lumbar fusion versus CMM, with a total of 72 patients in the control group, reported no complications over a 2-year follow-up.[114] Therefore, for the purpose of this report, it is assumed that patients on CMM do not experience either short-term or long-term complications.

In an observational clinical study that assessed clinical predictors of outcomes in 410 SCS patients, Kumar *et al*.[113] reported an annual SCS withdrawal (explantation) rate of 3.24%. This withdrawal rate from SCS was reported to be the result of loss of satisfactory pain relief despite corrective procedures, refusal of the patient to undergo corrective procedures and gradual loss of satisfactory pain relief (with technically functioning electrodes).

Costs and resources used

SCS costs

A detailed review is undertaken to obtain the most recent evidence on costs for the different health states. Unfortunately, the costs from the PROCESS trial[115] are academic in confidence and therefore resource-use evidence is taken from other sources as outlined below. Medication costs are taken from the 2007 *British National Formulary*,[116] costs for general practitioner visits are taken from Curtis and Netten[107] and other costs are adjusted to 2007 £s.

Trial stimulation The cost of trial stimulation is calculated considering the resource use presented in a Canadian retrospective analysis conducted by Kumar *et al*. that includes the cost for consultation, investigations, surgery, electrode and hospital charges.[117] The unit prices are substituted with UK costs obtained from the NHS reference costs and from Curtis and Netten.[118] The consultation cost consists of psychiatrist, social worker, general practitioner, neurosurgeon,

TABLE 26 *Six-month success probabilities*

		Number of successful participants after SCS trial stimulation	Probability of trial stimulation success	Number of patients that achieved ≥ 50% pain relief	Probability of achieving ≥ 50% pain relief
FBSS: SCS vs CMM					
PROCESS	SCS (n = 52)	43	0.827 (43/52)	24	0.585 (24/41[a])
	CMM (n = 48)	NA	NA	4	0.091 (4/44[b])
FBSS: SCS vs reoperation					
North	SCS (n = 23)	17	0.739 (17/23)	17	1.00 (17/17)
	Reoperation (n = 26)	NA	NA	12	0.462 (12/26)
CRPS: SCS vs CMM					
Kemler	SCS (n = 36)	24	0.667 (24/36)	18	0.750 (18/24)
	CMM			None reported	0.444 (assumed)

NA, not applicable.
a From 43 successful trial participants two withdrew consent.
b From 48 patients, four withdrew consent.

neurologist, orthopaedic surgeon and follow-up during trial (nurse) costs. The investigation cost consists of computed tomography, magnetic resonance imaging, radiography and myelography. The surgery cost is based on anaesthesia and neurosurgical fees. The estimated total cost per patient for SCS trial is £4156.

Implantation The cost of device implant is based on the costs of consultation, investigations, surgery, device, electrodes, in-line connector and hospital admissions. Consultation, investigation and surgery costs are defined as above.[117] The estimated implantation cost per patient is £10,066.

Complications The cost for complications is calculated based on fractured electrode, displaced electrode, hardware malfunction, biological and infection costs, taken from Kumar *et al*.[117] and adjusted to 2007 £s using the Pay and Prices annual percentage increase.[107] The estimated complication average cost per patient per annum is £393.

Device explantation and failed trial stimulation It is assumed that the cost of failed trial stimulation is the same as the cost for device explant. The device explant is calculated considering the resource use presented in Kumar *et al*.[117] where each patient visits the general practitioner twice (one initial visit and one follow-up visit) and has a neurosurgical consultation, surgeon's fee and hospital charges. The estimated explantation cost is £1041.

Conventional medical management costs

During the first 6 months in the PROCESS trial,[59] patients under CMM had drug and non-drug treatments. The drug treatment comprised opioids, NSAIDs, antidepressants and antiepileptics. *Table 27* shows the percentage of patients that were taking each drug treatment.

The non-drug treatments for pain reported in the PROCESS trial are physical rehabilitation, psychological rehabilitation, acupuncture, massage and transcutaneous electrical stimulation of nerves.[59] The percentage of patients undergoing these therapies is presented in *Table 28*.

The costs of physical rehabilitation (£40) and psychological rehabilitation (£40) per hour of client contact are taken from Curtis and Netten.[107] The cost of acupuncture is taken from Ratcliffe *et al.*[119] and adjusted to 2007 £s. Ratcliffe *et al.*[119] evaluated the cost-effectiveness of acupuncture in the management of persistent non-specific low back pain. The estimated unit cost of acupuncture treatment is £31.50. It is assumed that the cost of massage and the cost of acupuncture are the same.

TABLE 27 *Drug therapy resource use*[59]

	SCS (% patients)	CMM (% patients)
Opioids	56%	70%
NSAIDs	34%	50%
Antidepressants	34%	55%
Anticonvulsants	26%	50%

TABLE 28 *Non-drug therapy resource use*[59]

	SCS (% patients)	CMM (% patients)	Average unit frequency
Physical rehabilitation	6%	18%	
Psychological rehabilitation	2%	11%	
Acupuncture	0%	7%	10.6[a]
Massage	0%	9%	10.1[a]
Transcutaneous electrical stimulation of nerves	0%	11%	

a Number of sessions over 6 months.

A 5-year Canadian cost-effectiveness analysis of treatment of chronic pain with SCS versus CMM showed that the cost of CMM in year 2 was reduced by 17.8% compared to the cost in year 1.[111] This is taken from a clinical study with a control group of 44 patients where resource consumption data were collected. The costs of CMM were calculated using the following parameters: physician fees, drugs, radiological investigations (e.g. computed tomography, radiography, etc), alternative therapies (e.g. massage, physiotherapy and chiropractic treatments) and hospital admissions. Therefore, it is assumed that the annual cost of CMM in year 2 is reduced by 17.8% compared to the cost of year 1. After year 2 the cost of CMM remains constant.

The cost of CMM during the first 6 months is £3469 whereas the cost of CMM for patients with an SCS implant is £1720. The annual costs of CMM (£3440) for patients with an SCS implant remains constant whereas the cost of CMM for the first year is £6936. The annual cost of CMM for subsequent years is £5704 (because of the 17.8% reduction discussed above).

Reoperation costs

The reoperation cost (£4252) is taken from the NHS National Tariff R09 (revisional spinal procedures).[112]

CRPS

It is assumed that the drug and non-drug costs for CMM in CRPS are equivalent to those costs for CMM in FBSS. Clinical experts reported that CMM for both indications (FBSS and CRPS) includes opioids, antineuropathic pain drugs, physiotherapy, psychology and occasional nerve block. Therefore, it was agreed that the costs of drug treatments in CRPS were similar to those of FBSS.

Health-related quality of life utility by health state

A literature review was carried out to obtain the most appropriate and recent published evidence on utility measures for the health states modelled (Appendix 2).

The criteria used to evaluate the identified studies are as follows:

- use of a preference-based utility instrument (EQ-5D, in the UK)[110]
- UK setting studies are preferred to non-UK studies
- patients suffering from neuropathic pain.

There is a dearth of published evidence reporting quality of life measurements for individuals with chronic neuropathic pain. Utility values for FBSS are based on those reported in the PROCESS trial.[59] The utility for no pain relief health state is assumed to be equal to the baseline utility across all patients. It is found that having a complication reduced the utility values by 0.07 (*Table 29*).

A study by McDermott *et al.*[16] investigated the burden of neuropathic pain in a cross-sectional survey of 602 patients recruited from general practitioners in six European countries: France, Germany, Italy, the Netherlands, Spain and the United Kingdom. The population comprised adult patients (> 18 years old) with at least a 1-month history of the condition who had experienced symptoms in the week before the survey. The patient questionnaire included the Brief Pain Inventory, the EQ-5D, and questioned productivity, non-drug treatment and frequency of physician visits. Most patients reported moderate (54%) or severe (25%) pain. There was a significant association ($p < 0.001$) between pain severity and EQ-5D scores. The scores for mild, moderate and severe pain severity were 0.67, 0.46 and 0.16,

TABLE 29 *Health-state utility values used in the model*[16,59]

Health state	Utility value	
	FBSS	CRPS
Optimal pain relief with no complications	0.598	0.67
Optimal pain relief + complications	0.528	0.62
Suboptimal pain relief with no complications	0.258	0.46
Suboptimal pain relief + complications	0.258	0.41
No perceived pain reduction	0.168	0.16

respectively. In this ScHARR economic evaluation, it is assumed that in CRPS for optimal pain relief, the utility value is 0.67, for suboptimal pain relief the utility value is 0.46 and no pain relief has a utility value of 0.16. These figures suggest that the benefit achieved from having a pain reduction of at least 50% is approximately 0.5 utility units, showing that the prevailing factor in utility values is level of pain.

Taylor and Taylor[108] reported a utility loss associated with SCS complication (e.g. infection, electrode or lead problems) as –0.05 utility units. This was applied to both optimal and suboptimal pain relief health states. *Table 29* presents the utility values used in this economic assessment.

Mortality

National statistics were accessed online to obtain the proportion of patients dying from all causes.[36] The death rate per annum is 0.94%.

Key modelling assumptions

A summary of the key modelling assumptions is provided below.

- Optimal pain relief is defined as achieving at least 50% of pain relief from baseline, measured by VAS.
- Suboptimal pain relief is defined as achieving less than 50% of pain relief from baseline, measured by VAS.
- No patient dies within the first 6 months (short-term decision tree).
- Patients, when entering the Markov process remain in the same health state (optimal or suboptimal pain relief) as they were at the end of the first 6 months (short-term decision tree model).
- It is assumed that patients on CMM do not experience either short-term or long-term complications.[114]
- It is assumed that after 6 months complications in SCS occur at a rate of 18% per annum.[49]
- It is assumed that the cost of device explant is the same as the cost of failed trial stimulation.
- It is assumed that the cost of acupuncture is the same as the cost of massage.[119]
- It is assumed that the annual cost of CMM in year 2 is reduced by 17.8% compared to the cost of year 1.[111]
- After year 2 the cost of CMM remains constant.
- It is assumed that the drug and non-drug costs for CMM in CRPS are equivalent to those costs for CMM in FBSS.
- Annual SCS withdrawal rate is 3.24%.[113]
- The model explores the cost and benefits accrued through pain relief over a 15-year period.[113]
- In FBSS, the utility for the no pain relief health state was assumed to be equal to the baseline utility across all patients (0.168).[59]
- In CRPS, the utility values were taken from a cross-sectional survey that investigates the burden of neuropathic pain.[16]
- The transitions from health states are presented in Table 30 and are based on the assumptions discussed above.

Cost-effectiveness ratios

The ICERs measure the additional cost per QALY gained of Treatment A versus Treatment B such that ICER = (Cost of Treatment A – Cost of Treatment B)/(Utility of Treatment A – Utility of Treatment B).

Ischaemic pain

A mathematical model is developed to explore the cost and health outcomes of SCS in the treatment of refractory angina using a UK NHS perspective. The health economic analysis undertaken estimates the incremental cost-effectiveness ratios of SCS in combination with conventional management treatment in comparison with coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) or CMM. A threshold analysis is presented because of the dearth of direct clinical evidence. This analysis attempts to clarify the

TABLE 30 *Annual transition probabilities*

	Failing SCS (no pain relief)	Suboptimal	Surgery	Optimal pain relief (CMM)	Death
Optimal SCS	3.24%	0.00%			0.94%
Suboptimal SCS	3.24%				0.94%
Optimal CMM		0.00%			
Suboptimal CMM			5.00%		0.94%
Surgery				19.00%	

impact of overall survival benefit of SCS on cost-effectiveness and cost-utility levels of acceptability. This model should be interpreted bearing in mind the absence of available evidence on the comparative efficacy of SCS versus CABG, PCI and CMM, as previously discussed in Chapter 3. This model is also centred on the clinical appropriateness criteria used to inform decisions about practice.

Population considered in the ScHARR economic evaluation

The model is based on a prospective observational study that compares the cost-effectiveness of CABG, PCI or CMM.[120] Consecutive, unselected patients who had undergone coronary angiography between April 1996 and April 1997 at three hospitals of one NHS Trust in London were recruited. A total of 4121 patients were identified and followed for 6 years. From these patients, a subgroup of 1740 patients was rated appropriate to have CABG ($n = 815$), PCI ($n = 385$) or both revascularisation procedures ($n = 520$). Twenty patients were excluded because they died before undergoing revascularisation. Clinical judgement and available evidence were used to define appropriateness using a nine-member Delphi panel.[121] Approximately 70% of the 1720 had a Canadian Cardiovascular Society (CCS) score III–IV (severe angina). Hence, it could be assumed that the population of this study was representative of patients with refractory angina.[120] Three different scenarios based on clinical appropriateness were defined:

- scenario 1: patients clinically appropriate to receive CABG
- scenario 2: patients clinically appropriate to receive PCI
- scenario 3: patients clinically appropriate to receive both revascularisation procedures (CABG and PCI).

Treatment/comparator

Comparator 1: CABG

Coronary artery bypass grafting is defined as a revascularisation procedure and is a standard treatment in severe angina pectoris. CABG patients also receive CMM.

Comparator 2: PCI

Percutaneous coronary intervention is defined as a revascularisation procedure and is a standard treatment in severe angina pectoris. PCI patients also receive CMM.

Comparator 3: CMM

The medical therapy basically consists of short-acting nitrates, beta-blockers, anticoagulants angiotensin-converting enzyme inhibitors, long-acting nitrates, calcium channel inhibitors and aspirin.[80]

Table 31 presents the distribution of patients in each of the three scenarios and three comparators (management) defined above.

Time horizon

The model explores the costs and benefits accrued through pain relief over a 6-year period. This timeframe is taken from an observational clinical study that assesses clinical predictors of outcomes in patients who received CABG, PCI or both revascularisation procedures in the treatment of angina pectoris.[120]

Perspective

A UK NHS perspective is used, therefore productivity lost through illness or costs incurred directly by patients are not included. Discount rates of 3.5% are applied to both costs and health benefits, according to current NICE guidelines.[110] Costs are at 2007 prices.

Costs and resources used

SCS costs

A detailed review was undertaken to obtain the most recent evidence on costs for the different comparators. Medication costs are taken from the 2007 British National Formulary,[116] costs for general practitioner visits are from Curtis and Netten[107] and other costs are adjusted to 2007 £s.

TABLE 31 *Number of patients by category and actual management*

	Received CABG	Received PCI	Received CMM
Appropriate for CABG ($n = 815$)	$n = 408$	$n = 54$	$n = 353$
Appropriate for PCI ($n = 385$)	$n = 149$	$n = 173$	$n = 198$
Appropriate for both ($n = 520$)	$n = 45$	$n = 137$	$n = 203$

Implantation The cost of device implant is based on the costs of consultation, investigations, surgery, device, electrodes, in-line connector and hospital admissions. Consultation, investigation and surgery costs are defined as above.[117] The estimated implantation cost per patient is £10,479.

Coronary artery bypass grafting The cost for CABG at 6 years is taken from Griffin *et al.*[120] and adjusted to 2007 £s using the Pay and Prices annual percentage increase.[107] The estimated CABG average costs per patient at 6 years are presented in *Table 32*.

Percutaneous coronary intervention The cost for PCI at 6 years is taken from Griffin *et al.*[120] and adjusted to 2007 £s using the Pay and Prices annual percentage increase.[107] The estimated PCI average costs per patient at 6 years are presented in *Table 32*.

Conventional medical management costs

At 6 years the estimated CMM costs per patient are presented in *Table 32*. These costs are taken from Griffin *et al.*[120] and adjusted to 2007 £s using the Pay and Prices annual percentage increase.[107]

The ESBY trial that compares SCS versus CABG showed that the nitrate consumption on the SCS arm is reduced, after 6 months, by approximately 27% from baseline.[80] Hence, in the ScHARR's model, it is assumed that the annual cost of medication on SCS + CMM is reduced by 27% in year 1 and remains the same for the five following years. This can be an overestimated assumption because the ESBY trial reports a reduction in the use of nitrates only. Therefore, the costs of SCS + CMM are calculated by considering the cost of SCS implantation (£10,066) and the 73% of the cost of CMM reported by Griffin *et al.*[120] for each intervention (CABG, PCI, or both).

TABLE 32 *Estimated cost for CABG, PCI, CMM and SCS for three scenarios at 6 years[120]*

Scenario	Costs 2006–7 (£)[a]
1. Appropriate for CABG	
CABG	£18,000
PCI	£14,708
CMM	£11,502
SCS + CMM	£18,463
2. Appropriate for PCI	
CABG	£17,535
PCI	£12,183
CMM	£9302
SCS + CMM	£16,857
3. Appropriate for both	
CABG	£18,932
PCI	£14,848
CMM	£11,332
SCS + CMM	£18,339

a Discounted at rate 3.5% a year.

Health economic outcomes

ScHARR's model includes the following health economic outcomes:

- cost per life-year gained (LYG)
- cost per QALY gained.

Health-related quality of life utility

A literature review was carried out to obtain the most appropriate and recent published evidence on utility measures for the health states modelled (Appendix 2).

The criteria used to evaluate the identified studies are as follows:

- use of a preference-based utility instrument (EQ-5D, in the UK)[110]
- UK setting studies are preferred to non-UK studies
- patients suffering from severe angina.

The study by Griffin *et al.*[120] that investigated the cost-effectiveness of clinically appropriate decisions on treatments for angina pectoris presented utilities and QALYs at 6 years. Patients completed the EQ-5D health-related quality of life instrument, from which the utilities scores were derived (*Table 33*).

Results

Neuropathic pain model results

Results for the two primary indications (FBSS and CRPS) modelled in this assessment are presented in this section. All analyses use a 15-year time horizon. Results based on a device longevity ranging from 1 year to 15 years are presented in *Table 34*. The results are presented in discounted incremental values. The discounted and undiscounted costs and QALYs are provided in Appendix 10. The base case considers a device price of £7745. This price is the middle value

TABLE 33 *Health-state utility values and QALYs at 6 years used in the model*[120]

Scenario	Utility at 6 years	QALYs[a]
1. Appropriate for CABG		
CABG	0.69	3.29
PCI	0.61	3.01
CMM	0.67	3.02
2. Appropriate for PCI		
CABG	0.66	3.13
PCI	0.65	2.93
CMM	0.61	2.83
3. Appropriate for both		
CABG	0.69	3.08
PCI	0.65	3.31
CMM	0.66	3.15

a Discounted at rate 3.5% a year.

from the price list provided by two of the SCS manufacturers presented in Appendix 8.

Receiving a reimplant has an extra cost associated and therefore ICERs are sensitive to it. Kumar *et al.*[111] suggested that because of the lifespan of the pulse generator battery, these batteries needed replacement after 3.5 to 4.5 years. ABHI's model assumed that the pulse generator needs to be replaced once every 4 years. The *Physician Implant Manual* by the Advanced Bionics Corporation indicates that the projections for battery longevity are from 9.7 (highest impedance) to 11.3 (lowest impedance) years. Based on clinical advice the model considers average device longevity of 10 years as base case. From *Table 34*, it can be seen that with 8 years' longevity SCS + CMM dominates (cost less and accrued more benefits) the comparator strategy for all indications FBSS (CMM and reoperation) and CRPS.

From *Figure 7*, it can be seen that for FBSS (CMM alone and reoperation) with a device longevity of 1 year the ICERs are above £30,000, for a device longevity of 2 years the ICERs are below £30,000 while for a device longevity of 3 or more years the ICERs are below £20,000. In the CRPS indication with a device longevity of 3 years the ICERs are above £30,000 whereas for a device longevity of 5 or more years the ICERs are below £20,000. With a device longevity of 4 years the ICER is £25,095 (*Table 34*).

TABLE 34 *Results using different device longevity values*

	ICER (£/QALY)		
Device longevity (years)	FBSS:SCS + CMM vs CMM	FBSS:SCS + CMM vs reoperation	CRPS:SCS + CMM vs CMM
1	£61,612	£54,398	£186,923
2	£26,755	£23,536	£80,388
3	£13,105	£11,527	£40,017
4	£7996	£7043	£25,095
5	£3574	£3167	£12,264
6	£2913	£2588	£10,351
7	£2304	£2055	£8591
8	–£1267[a]	–£1071[a]	–£1701[a]
9	–£1492[a]	–£1269[a]	–£2349[a]
10	–£1707[a]	–£1456[a]	–£2965[a]
11	–£1910[a]	–£1634[a]	–£3549[a]
12	–£2103[a]	–£1803[a]	–£4104[a]
13	–£2287[a]	–£1964[a]	–£4632[a]
14	–£2461[a]	–£2116[a]	–£5133[a]
15	–£5787[a]	–£5024[a]	–£14,658[a]

a SCS + CMM dominates.

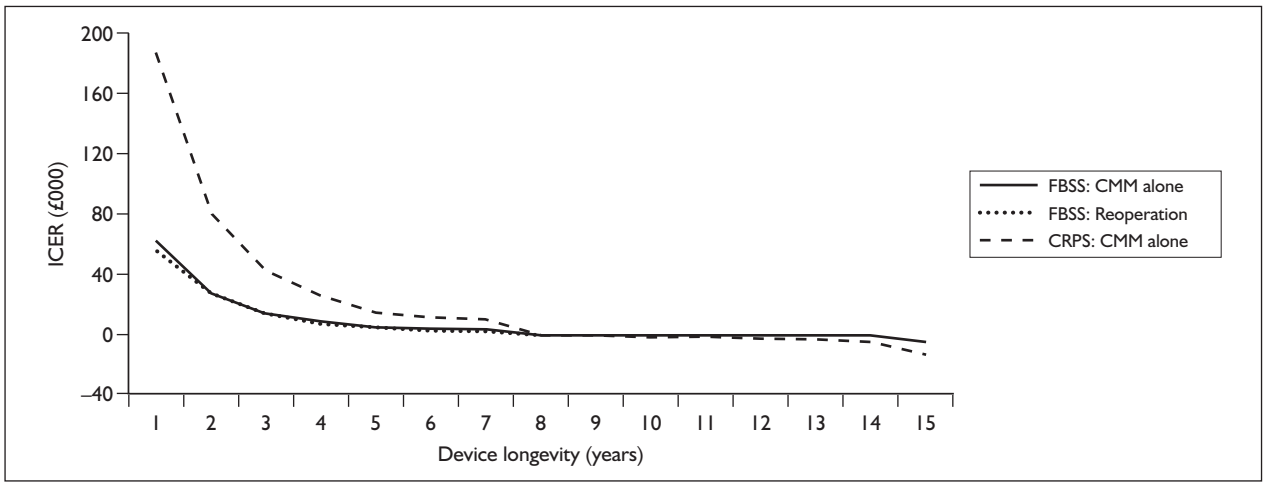

FIGURE 7 *Incremental cost-effectiveness ratios versus device longevity.*

Results for 15-year time horizon and 4-year device longevity

Table 35 shows the discounted cost and QALYs for each indication based on a 4-year device longevity and a 15-year time horizon. The results range from £7043 per QALY for FBSS (SCS + CMM versus reoperation) to £25,095 per QALY for CRPS (SCS + CMM versus CMM).

The results presented in *Table 35* suggest that SCS is expected to be more effective for FBSS than for CRPS. This analysis suggests that although SCS and CMM for CRPS are slightly less expensive than SCS and CMM for FBSS, the small difference between the effectiveness of SCS and CMM increases the incremental cost-effectiveness ratios (£25,095 per QALY).

Table 36 shows the discounted incremental costs and ICERs for each indication, at 6 months and every subsequent year until 15 years, based on a 4-year device longevity. The results suggest that for FBSS (CMM and reoperation) the ICERs are below £20,000 per QALY gained in year 3 onwards, although in year 5 the ICERs increase because of the costs incurred from having a battery replacement. Appendix 10 presents more detailed tables with discounted and undiscounted costs, QALYs and ICERs for each indication (FBSS and CRPS).

TABLE 35 *Results based on 4-year device longevity and 15-year time horizon*

FBSS: SCS + CMM vs CMM	***SCS + CMM***	***CMM***	***Difference***
Total discounted costs	£88,443	£78,408	£10,035
Discounted QALYs	5.30	4.05	1.26
ICER			£7996
FBSS: SCS + CMM vs reoperation	***SCS + CMM***	***Reoperation***	***Difference***
Total discounted costs	£87,674	£78,244	£9430
Discounted QALYs	6.94	5.60	1.34
ICER			£7043
CRPS: SCS + CMM vs CMM	***SCS + CMM***	***CMM***	***Difference***
Total discounted costs	£86,280	£77,505	£8775
Discounted QALYs	7.71	7.36	0.35
ICER			£25,095

TABLE 36 *ICERs based on 4-year device longevity at 6 months and every subsequent year until 15 years*

	FBSS: SCS + CMM vs CMM			FBSS: SCS + CMM vs reoperation			CRPS: SCS + CMM vs CMM		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
6 months	£10,598	0.064	£165,247	£9368	0.062	£150,803	£8746	0.016	£542,898
Year 1	£9252	0.130	£71,010	£8140	0.129	£63,201	£7686	0.035	£219,597
Year 2	£7630	0.256	£29,855	£6682	0.256	£26,114	£6425	0.071	£90,842
Year 3	£6090	0.372	£16,359	£5297	0.375	£14,113	£5229	0.104	£50,288
Year 4	£4628	0.481	£9624	£3982	0.488	£8167	£4093	0.135	£30,343
Year 5	£10,227	0.580	£17,630[a]	£9264	0.590	£15,698[a]	£8646	0.162	£53,447[a]
Year 6	£8910	0.674	£13,221	£8078	0.689	£11,722	£7622	0.188	£40,458
Year 7	£7660	0.761	£10,065	£6952	0.782	£8890	£6649	0.213	£31,209
Year 8	£6473	0.842	£7690	£5883	0.869	£6768	£5725	0.236	£24,273
Year 9	£11,042	0.915	£12,067[a]	£10,191	0.949	£10,743[a]	£9439	0.255	£36,950
Year 10	£9973	0.984	£10,134	£9227	1.025	£9000	£8606	0.275	£31,307
Year 11	£8959	1.048	£8549	£8312	1.097	£7577	£7815	0.293	£26,691
Year 12	£7996	1.107	£7225	£7443	1.164	£6393	£7065	0.309	£22,842
Year 13	£11,725	1.160	£10,110[a]	£10,957	1.225	£8943[a]	£10,094	0.323	£31,234
Year 14	£10,858	1.209	£8977	£10,174	1.284	£7924	£9417	0.337	£27,943
Year 15	£10,035	1.255	£7996	£9430	1.339	£7043	£8775	0.350	£25,095

a Increase in ICER due to battery replacement.

Another parameter that can impact the results is the cost of the SCS device. *Table 37* shows the ICERs for FBSS (SCS + CMM versus CMM) using a 4-year device longevity and a device costs range from £7000 to £14,000.

At any device cost in the range from £5000 to £14,000 and a device longevity of 4 years, the ICERs for the FBSS indications (CMM and reoperation) are below £20,000 per QALY. In the CRPS indication, when the device cost is £8000 the ICER is £26,555. When the device cost ranges from £9000 to £15,000, the ICERs are above £30,000 per QALY.

Figure 8 shows the trend of the incremental cost-effectiveness ratios for different SCS device costs. The cost-effectiveness estimates are more sensitive to the device cost with CRPS than with FBSS. The expected device cost to obtain ICERs below £30,000 per QALY is £8000.

Results for 15-year time horizon and variable device longevity and device cost

The most sensitive parameters are device longevity and device cost. *Table 38* presents the results when the parameters device longevity and device average price are varied simultaneously, for the FBSS indication (SCS + CMM versus CMM). The tables

TABLE 37 *Impact of device average price on incremental cost-effectiveness ratios*

	ICER (£/QALY)		
Device cost	**FBSS: SCS + CMM vs CMM**	**FBSS: SCS + CMM vs reoperation**	**CRPS: SCS + CMM vs CMM**
£5000	£2563	£2283	£9374
£6000	£4542	£4017	£15,101
£7000	£6521	£5751	£20,828
£8000	£8500	£7485	£26,555
£9000	£10,480	£9219	£32,282
£10,000	£12,459	£10,953	£38,010
£11,000	£14,438	£12,687	£43,737
£12,000	£16,418	£14,421	£49,464
£13,000	£18,397	£16,156	£55,191
£14,000	£20,376	£17,890	£60,918
£15,000	£22,356	£19,624	£66,646

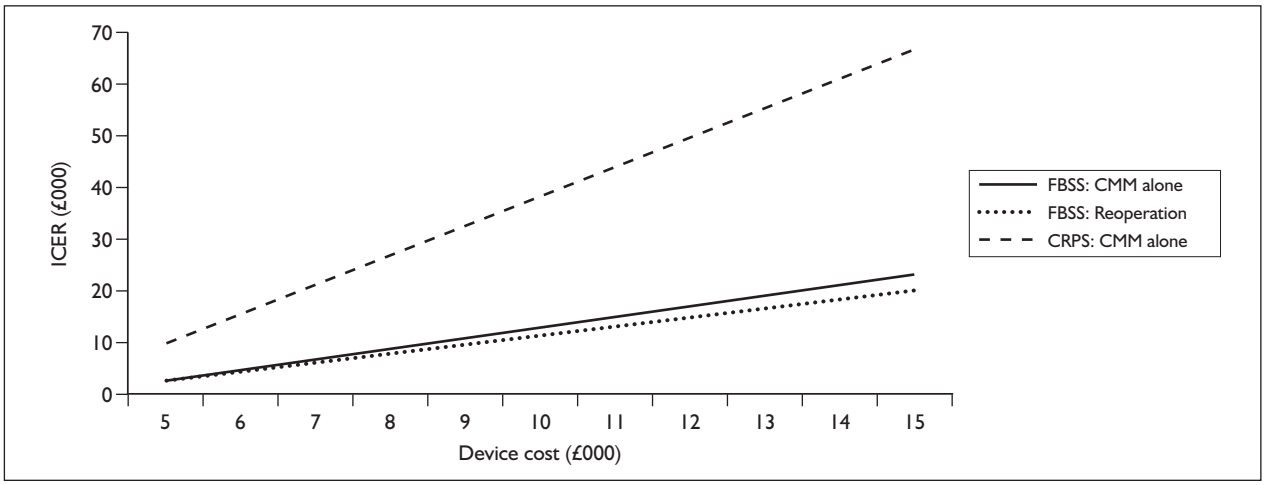

FIGURE 8 *Incremental cost-effectiveness ratios versus device cost.*

TABLE 38 *Impact of device average price and device longevity on ICER*

FBSS: SCS + CMM vs CMM alone	Discounted ICER (£/QALY)										
Device Cost/ Longevity	**£5,000**	**£6,000**	**£7,000**	**£8,000**	**£9,000**	**£10,000**	**£11,000**	**£12,000**	**£13,000**	**£14,000**	**£15,000**
1	£42,054	£49,179	£56,304	£63,429	£70,554	£77,679	£84,804	£91,929	£99,054	£106,179	£113,304
2	£16,380	£20,160	£23,940	£27,719	£31,499	£35,279	£39,059	£42,838	£46,618	£50,398	£54,178
3	£6326	£8796	£11,265	£13,735	£16,205	£18,674	£21,144	£23,614	£26,083	£28,553	£31,023
4	£2563	£4542	£6521	£8500	£10,480	£12,459	£14,438	£16,418	£18,397	£20,376	£22,356
5	−£694	£861	£2416	£3971	£5526	£7081	£8636	£10,191	£11,746	£13,301	£14,856
6	−£1181	£311	£1802	£3294	£4785	£6277	£7768	£9260	£10,751	£12,243	£13,734
7	−£1630	−£197	£1236	£2669	£4103	£5536	£6969	£8402	£9835	£11,268	£12,701
8	−£4260	−£3170	−£2079	−£989	£101	£1192	£2282	£3372	£4463	£5553	£6643
9	−£4426	−£3357	−£2289	−£1220	−£151	£918	£1986	£3055	£4124	£5192	£6261
10	−£4584	−£3536	−£2487	−£1439	−£391	£657	£1705	£2753	£3802	£4850	£5898
11	−£4734	−£3705	−£2676	−£1648	−£619	£410	£1438	£2467	£3496	£4524	£5553
12	−£4876	−£3866	−£2856	−£1846	−£836	£174	£1185	£2195	£3205	£4215	£5225
13	−£5011	−£4019	−£3026	−£2034	−£1041	−£49	£944	£1936	£2928	£3921	£4913
14	−£5140	−£4164	−£3188	−£2213	−£1237	−£261	£715	£1690	£2666	£3642	£4617

ICERs are below or very close to £30,000 per QALY for any device price from £7000 to £15,000 when the device longevity is 3 years. The ICER is below £20,000 per QALY for a device cost between £7000 and £15,000 if the device longevity is 4 years or more. Appendix 10 presents the ICERs for FBSS (SCS + CMM vs reoperation) and CRPS.

for FBSS (SCS + CMM versus reoperation) and CRPS are presented in Appendix 10.

Results for 15-year time horizon, 4-year device longevity and variable proportion of patients failing the test stimulation

According to RCTs the proportion of patients that are successful in the trial stimulation varies from 67% to 83%. The discounted ICER for FBSS (SCS + CMM versus CMM) with a success rate of 67% is £8190 per QALY while the ICER with a success rate of 82.7% is £7996 per QALY, suggesting that the impact of the proportion of patients failing the test stimulation on the overall ICERs is very small.

Probabilistic sensitivity analysis results

Comprehensive sensitivity analyses were undertaken to explore the joint uncertainty in model parameters on the cost-effectiveness of each indication (Appendix 9). Monte Carlo sampling techniques (10,000 samples) were used to generate information on the probability that each indication (FBSS: SCS versus CMM, FBSS: SCS versus reoperation, and CRPS: SCS versus CMM) is optimal in terms of amount of net benefit. The results of the probabilistic sensitivity analyses are presented as incremental cost-effectiveness acceptability curves (CEACs). *Table 39* below is a summary of the mean net benefit at thresholds of £20,000 per QALY gained and £30,000 per QALY gained for the base-case analysis (device price of £7745 and a 15-year time horizon). The 95% confidence interval indicates the uncertainty around the mean benefit.

FBSS: SCS + CMM versus CMM

The results of the probabilistic analysis using 15-year horizon and a base case using a 4-year device longevity and a device price of £7745 suggest that SCS + CMM compared to CMM alone produce more QALYs. The cost-effectiveness acceptability curve (*Figure 9*) shows that when using a threshold of £20,000 per QALY the probability of SCS + CMM being cost-effective is around 99.02%. Additionally, at a £30,000 per QALY threshold this probability is around 99.96%.

FBSS: SCS + CMM versus reoperation

The results found in the probabilistic analysis using the base case, suggest that SCS + CMM compared to reoperation produce more QALYs. The cost-effectiveness acceptability curve (*Figure 10*) shows that when using a threshold of £20,000 per QALY the probability of SCS + CMM being cost-effective is 100%.

CRPS: SCS + CMM versus CMM alone

The results of the probabilistic analysis, using a 15-year horizon, a 4-year device longevity and a device price of £7745, suggest that the probability of SCS + CMM being cost-effective at a £20,000 per QALY threshold is around than 78.36% (*Figure 11*). Additionally, at a £30,000 per QALY threshold this probability is around 97.38%.

Ischaemic pain model results

This section reports the results of the cost-effectiveness analysis of SCS in the treatment of refractory angina. There is a lack of evidence demonstrating whether SCS improves the overall survival compared with revascularisation (CABG or PCI) or medical treatment so the results are presented as a threshold analysis. This

TABLE 39 *Impact of device average price and device longevity on ICER*

	Standard deviation net benefit	Mean net benefit	95% CI for mean net benefit		Distribution (95% CI) for net benefit	
£20,000 per QALY						
FBSS: SCS + CMM vs CMM alone	6058	£12,414	£12,246	£12,582	£1541	£25,154
FBSS: SCS + CMM vs reoperation	5409	£14,171	£14,021	£14,321	£4915	£25,613
CRPS: SCS + CMM vs CMM alone	4420	£3548	£3425	£3671	−£3547	£13,705
£30,000 per QALY						
FBSS: SCS + CMM vs CMM alone	9067	£24,358	£24,107	£24,609	£8372	£42,972
FBSS: SCS + CMM vs reoperation	8317	£26,439	£26,208	£26,670	£11,840	£43,669
CRPS: SCS + CMM vs CMM alone	6521	£10,239	£10,058	£10,420	−£133	£25,325

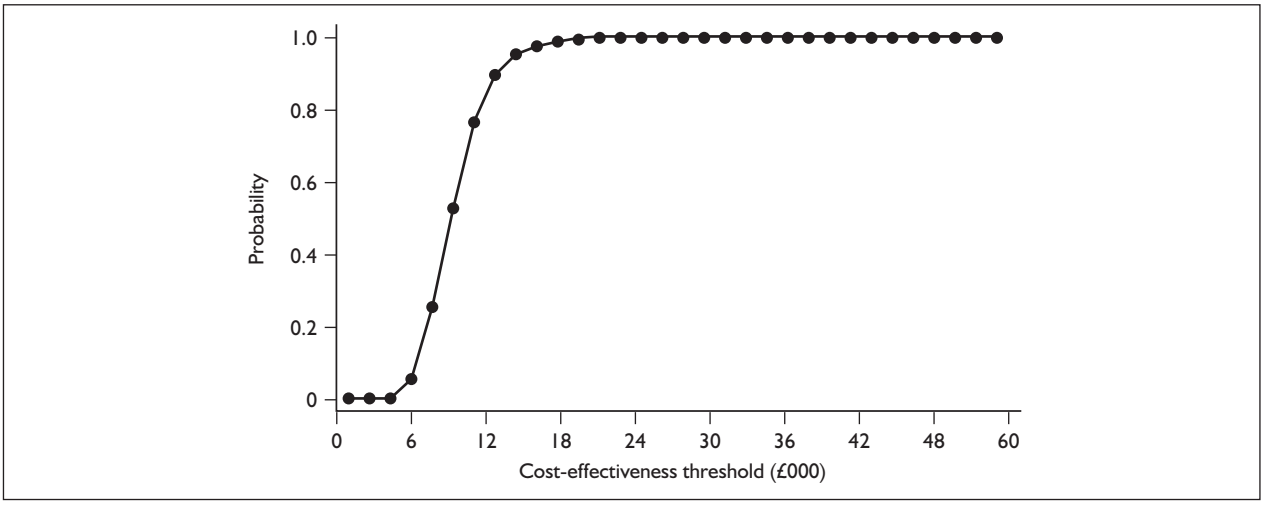

FIGURE 9 *Cost-effectiveness acceptability curve for FBSS: SCS + CMM versus CMM.*

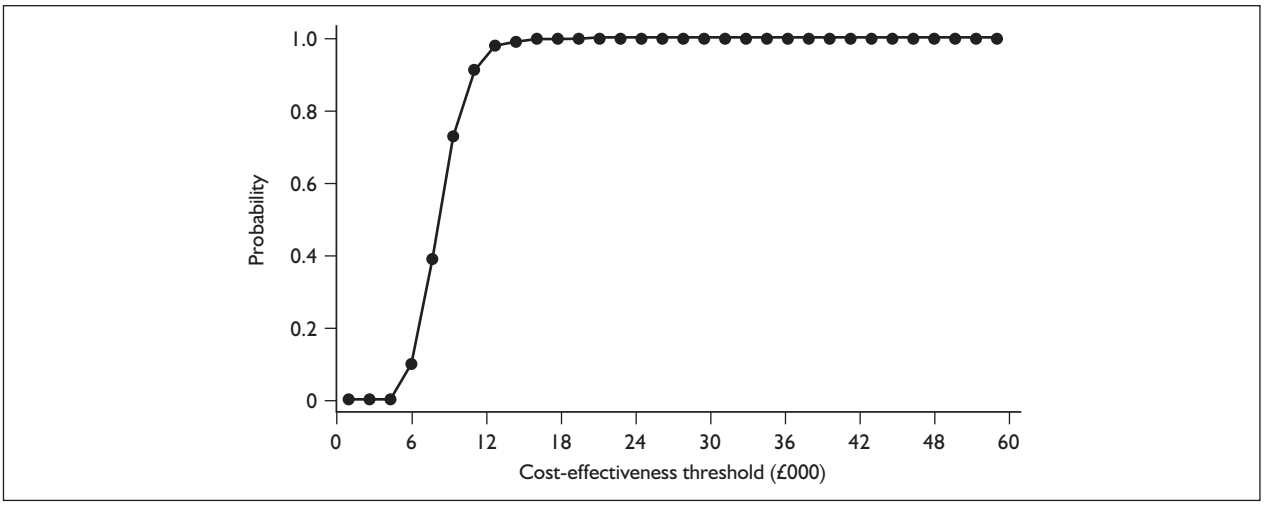

FIGURE 10 *Cost-effectiveness acceptability curve for FBSS: SCS + CMM versus reoperation.*

analysis presents the necessary improvement that patients receiving an SCS implant would have to demonstrate to achieve certain levels of incremental cost–utility or cost-effectiveness. The results are presented for three different scenarios defined in terms of clinical appropriateness:

- patients clinically appropriate to receive CABG
- patients clinically appropriate to receive PCI
- patients clinically appropriate to receive both revascularisation procedures.

Scenario 1: Patients clinically appropriate to receive CABG

Figure 12 presents the incremental difference of SCS + CMM compared with CABG, PCI and CMM. The vertical axis represents the incremental survival benefit due to SCS + CMM versus revascularisation (CABG or PCI) or CMM and the horizontal axis shows the incremental cost per LYG.

Figure 12 shows that for patients who are clinically appropriate to receive CABG, SCS + CMM must provide an additional 0.0235 life-years when compared with CABG to achieve £20,000 per LYG and 0.0155 additional life-years to achieve £30,000 per LYG. SCS + CMM must provide an additional 0.185 life-years when compared with PCI to achieve an incremental cost per LYG of £20,000 and at least 0.125 additional life-years to achieve incremental costs per LYG below £30,000. The model suggests that SCS + CMM must provide at least an additional 0.35 life-years when compared with CMM to achieve incremental costs per LYG below £20,000. *Figure 12* shows that SCS + CMM

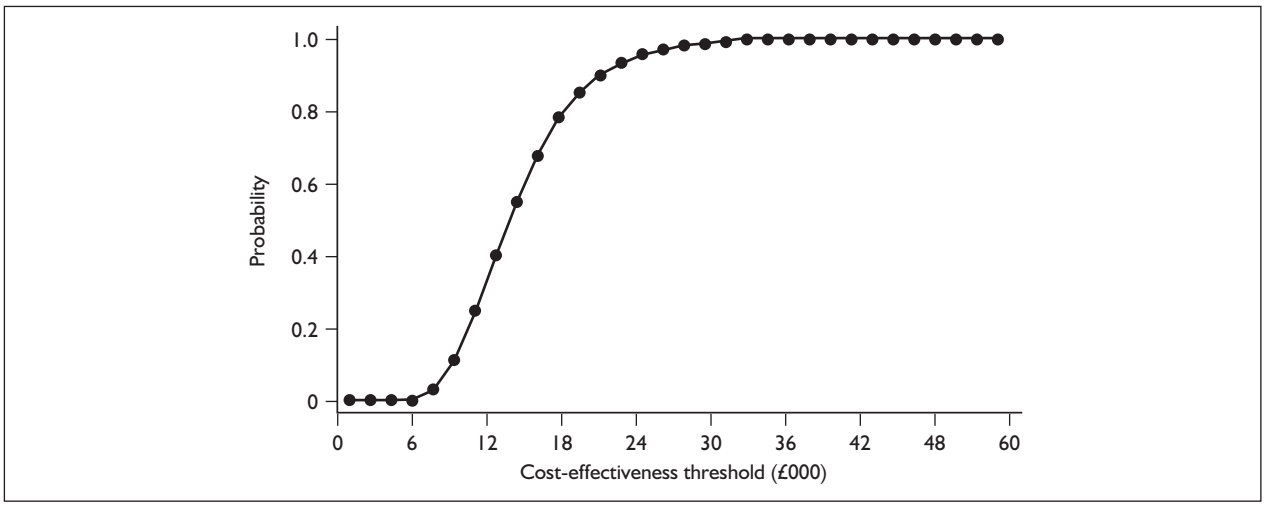

FIGURE 11 *Cost-effectiveness acceptability curve for CRPS: SCS + CMM versus CMM.*

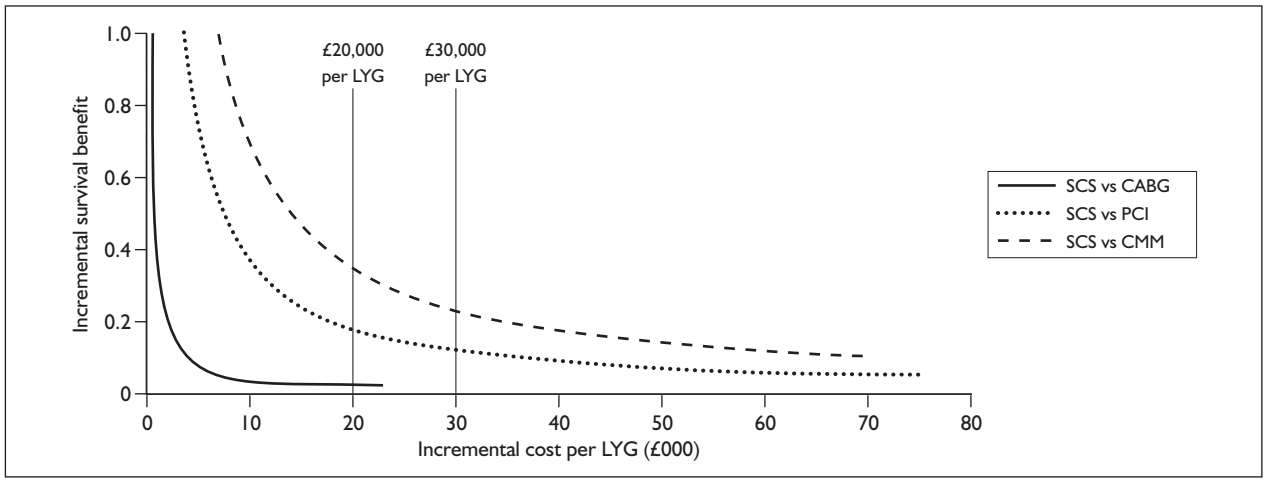

FIGURE 12 *Threshold analysis in terms of incremental cost per LYG.*

should provide an additional 0.23 additional life-years to achieve an incremental cost per LYG of £30,000.

Figure 13 presents the incremental cost-effectiveness ratios of SCS + CMM compared with CABG, PCI and CMM. The horizontal axis represents the incremental QALYs due to SCS + CMM versus revascularisation (CABG or PCI) or CMM and the vertical axis shows the ICERs.

Table 40 shows that for patients who are clinically appropriate to receive CABG, SCS + CMM must provide at least an additional 0.0231 and 0.0154 QALYs when compared to CABG to achieve ICERs of £20,000 and £30,000 per QALY gained, respectively. Therefore, the SCS utility value to achieve an ICER of £20,000 per QALY is 0.6218 whereas the utility value should be 0.6203 to achieve £30,000 per QALY gained. SCS + CMM must provide at least an additional 0.1877 and 0.1251 QALYs when compared to PCI to achieve ICERs of £20,000 and £30,000 per QALY gained, respectively. Therefore, the SCS utility value to achieve an ICER of £20,000 per QALY is 0.6001 whereas the utility value is 0.5884 to achieve £30,000 per QALY gained. *Table 40* also shows that SCS + CMM must provide at least an additional 0.3480 and 0.2320 QALYs when compared with CMM to achieve ICER of £20,000 and £30,000 per QALY gained, respectively. The SCS utility value to achieve an ICER of £20,000 per QALY is 0.6321

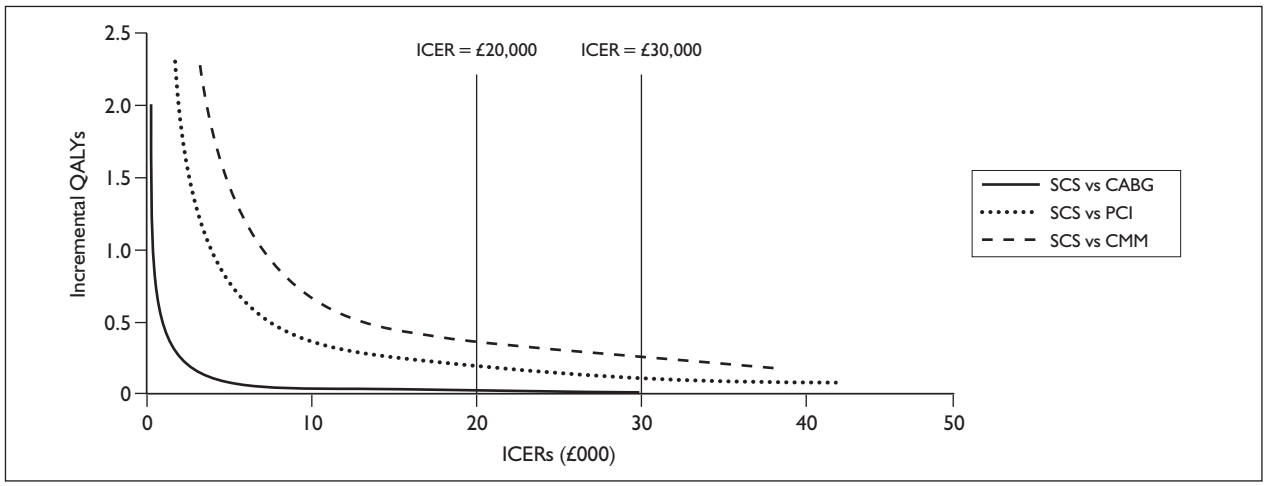

FIGURE 13 *Threshold analysis in terms of incremental cost per QALYs.*

TABLE 40 *Threshold analysis in terms of incremental cost per QALY and utility values*

	SCS vs CABG		SCS vs PCI		SCS vs CMM	
Threshold	£20,000	£30,000	£20,000	£30,000	£20,000	£30,000
Incremental QALY	0.0231	0.0154	0.1877	0.1251	0.3480	0.2320
SCS QALY	3.3131	3.3054	3.1977	3.1351	3.3680	3.2520
SCS utility	0.6218	0.6203	0.6001	0.5884	0.6321	0.6103

whereas the utility value is 0.6103 to achieve £30,000 per QALY gained.

Scenario 2: Patients clinically appropriate to receive PCI

For patients who are clinically appropriate to receive PCI, SCS + CMM dominates in terms of cost per LYG when compared with CABG. This means that SCS cost less and accrued more survival benefits. The model suggests that in terms of incremental cost-effectiveness ratios (£/QALY), SCS + CMM is dominant when the incremental QALYs are in the range from 2.25 to 0.12.

Figure 14 presents the incremental difference of SCS + CMM compared with PCI and CMM. The vertical axis represents the incremental survival benefit due to SCS + CMM versus revascularisation (PCI) or CMM and the horizontal axis shows the incremental cost per LYG.

The model suggests that SCS + CMM must provide an additional 0.235 life-years when compared with PCI to achieve an incremental cost per LYG of £20,000 and at least 0.155 additional life-years to achieve incremental costs per LYG below £30,000. SCS + CMM must provide at least an additional 0.38 life-years when compared with CMM to achieve incremental costs per LYG below £20,000. *Figure 14* shows that SCS + CMM should provide an additional 0.25 to achieve an incremental cost per LYG of £30,000.

Figure 15 presents the incremental cost-effectiveness ratios of SCS + CMM compared with PCI and CMM. The vertical axis represents the incremental QALYs due to SCS + CMM versus revascularisation (CABG or PCI) or CMM and the horizontal axis shows the ICERs.

Table 41 shows that for patients who are clinically appropriate to receive PCI, SCS + CMM must provide at least an additional 0.2337 and 0.1558 QALYs when compared with PCI to achieve ICERs of £20,000 and £30,000 per QALY gained, respectively. Therefore, the SCS utility value to achieve an ICER of £20,000 per QALY is 0.6650 whereas the utility value is 0.6504 to achieve £30,000 per QALY gained. SCS + CMM must provide at least an additional 0.3777 and 0.2518 QALYs when compared to CMM to achieve ICERs of £20,000 and £30,000 per QALY gained,

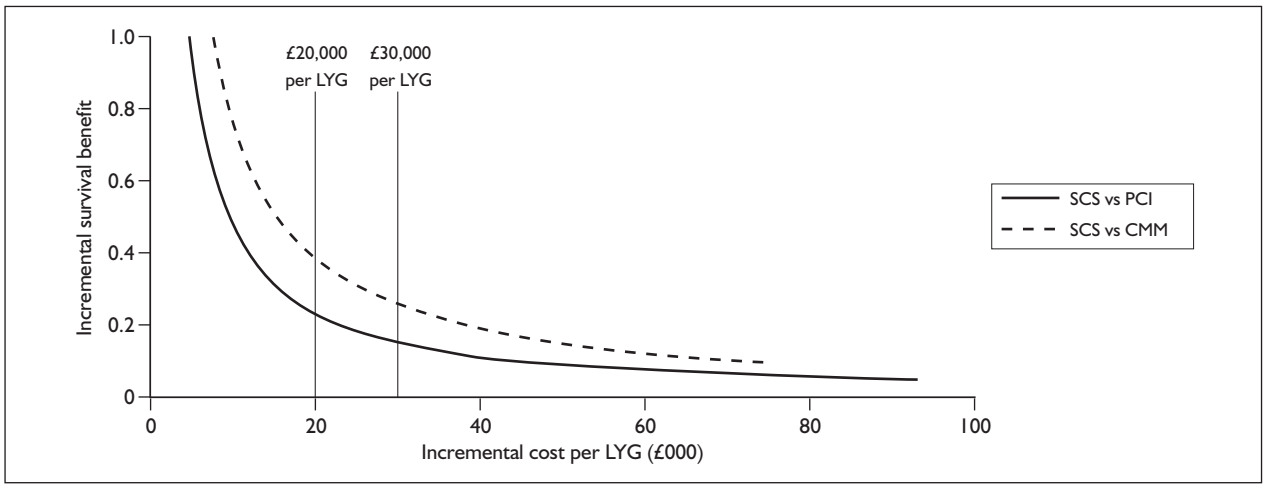

FIGURE 14 *Threshold analysis in terms of incremental cost per LYG.*

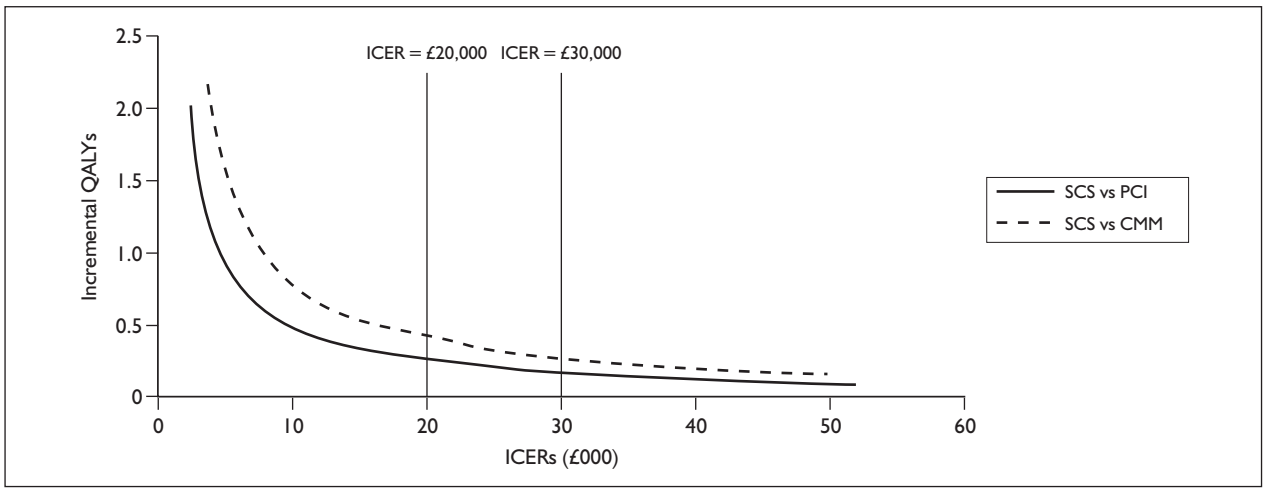

FIGURE 15 *Threshold analysis in terms of incremental cost per QALYs.*

TABLE 41 *Threshold analysis in terms of incremental cost per QALY and utility values*

	SCS vs PCI		SCS vs CMM	
Threshold	£20,000	£30,000	£20,000	£30,000
Incremental QALY	0.2337	0.1558	0.3777	0.2518
SCS QALY	3.5437	3.4658	3.5277	3.4018
SCS utility	0.6650	0.6504	0.6620	0.6384

respectively. The SCS utility value to achieve an ICER of £20,000 per QALY is 0.6620 whereas the utility value is 0.6384 to achieve £30,000 per QALY gained.

Scenario 3: Patients clinically appropriate to receive both revascularisation procedures

For patients who are clinically appropriate to

receive CABG and PCI, SCS + CMM dominates in terms of cost per LYG when compared with CABG. This means that SCS cost less and accrued more survival benefits. The model suggests that in terms of incremental cost-effectiveness ratios, SCS + CMM is dominant when the incremental QALYs are in a range from 2.20 to 0.07.

Figure 16 presents the incremental difference of SCS + CMM compared with PCI and CMM. The vertical axis represents the incremental survival benefit due to SCS + CMM versus revascularisation (PCI) or CMM and the horizontal axis shows the incremental cost per LYG.

The model suggests that SCS + CMM must provide an additional 0.1 life-years when compared with PCI to achieve an incremental cost per LYG of £20,000 and at least 0.067 additional life-years to achieve incremental costs per LYG below £30,000. SCS + CMM must provide at least an additional 0.275 life-years when compared with CMM to achieve incremental costs per LYG below £20,000. *Figure 16* shows that SCS + CMM should provide an additional 0.185 to achieve an incremental cost per LYG of £30,000.

Figure 17 presents the incremental cost-effectiveness ratios of SCS + CMM compared with PCI and CMM. The vertical axis represents the incremental QALYs due to SCS + CMM versus revascularisation (CABG or PCI) or CMM and the horizontal axis shows the ICERs.

Table 42 shows that for patients who are clinically appropriate to receive CABG and PCI, SCS + CMM must provide at least an additional 0.1004 and 0.0669 QALYs when compared with PCI to achieve

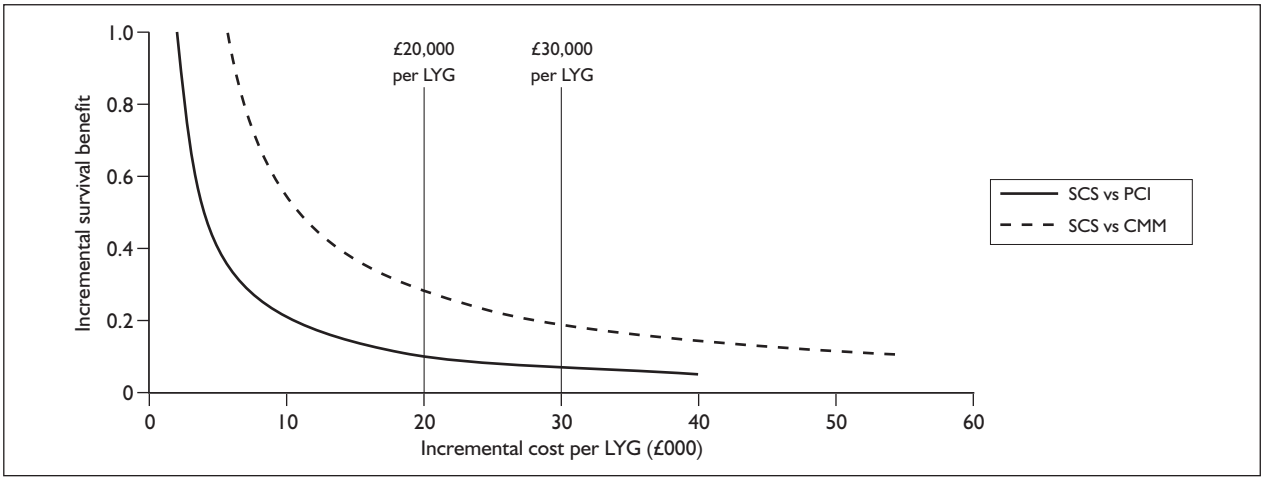

FIGURE 16 *Threshold analysis in terms of incremental cost per LYG.*

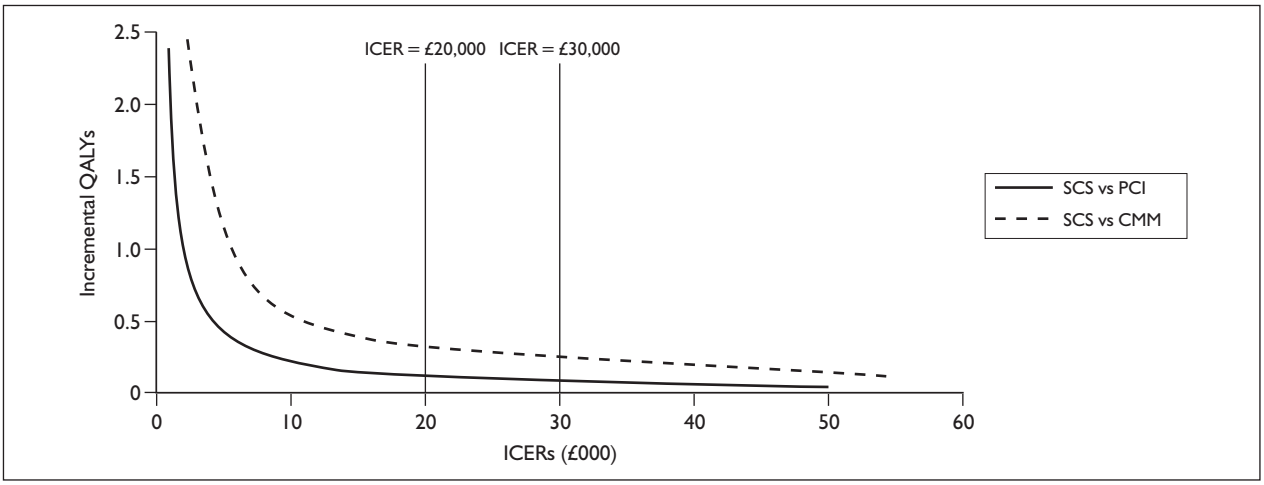

FIGURE 17 *Threshold analysis in terms of incremental cost per QALYs.*

TABLE 42 *Threshold analysis in terms of incremental cost per QALY and utility values*

	SCS vs PCI		SCS vs CMM	
Threshold	£20,000	£30,000	£20,000	£30,000
Incremental QALY	0.1004	0.0669	0.2762	0.1842
SCS QALY	3.0304	2.9969	3.1062	3.0142
SCS utility	0.5687	0.5624	0.5829	0.5657

ICERs of £20,000 and £30,000 per QALY gained, respectively. Therefore, the SCS utility value to achieve an ICER of £20,000 per QALY is 0.5687 whereas the utility value is 0.5624 to achieve £30,000 per QALY gained. SCS + CMM must provide at least an additional 0.2762 and 0.1842 QALYs when compared with CMM to achieve ICERs of £20,000 and £30,000 per QALY gained, respectively. The SCS utility value to achieve an ICER of £20,000 per QALY is 0.5829 whereas the utility value is 0.5657 to achieve £30,000 per QALY gained.

Discussion of results

Neuropathic pain model summary of key results

The results over a 15-year time horizon, a device longevity of 4 years and a device cost of £7745, suggest that the cost-effectiveness estimates for SCS intervention in patients with FBSS who have an inadequate response to medical or surgical treatment are below £20,000 per QALY gained. In patients with CRPS who have had an inadequate response to medical treatment the incremental cost-effectiveness ratio is £25,095 per QALY gained.

When the device longevity is greater than 3 years the results show that the cost-effectiveness estimates for SCS intervention for patients with FBSS (compared with CMM alone and reoperation) are below a threshold of £20,000 per QALY gained. In CRPS (compared with CMM alone) when using a device longevity of 3 years the ICER is £40,017 per QALY gained.

When the SCS device costs vary in a range from £5000 to £15,000, the ICERs range from £2563 per QALY to £22,356 per QALY for patients with FBSS when compared with CMM alone and from £2283 per QALY to £19,624 per QALY for patients with FBSS when compared with reoperation. For patients with CRPS the ICERs range from £9374 per QALY to £66,646 per QALY. In the CRPS indication, the maximum average price for a device to remain under an estimated ICER of £20,000 per QALY is £6000, and £8000 to remain under £30,000 per QALY.

If the device longevity (1 to 14 years) and the device average price (£5000 to £15,000) are varied simultaneously, the ICERs are below or very close to £30,000 per QALY when the device longevity is 3 years. Even more, the ICERs are below or very close to £20,000 per QALY when the device longevity is 4 years. Several sensitivity analyses are performed varying the costs of CMM, device longevity and average device cost. From the sensitivity analyses results, it can be seen that the ICERs for the CRPS indication are higher. The trial from which the effectiveness evidence (Kemler *et al.*[122]) is based, compares SCS to a specific physical therapy that might be different to the one administered by the NHS. Hence, this may be translated as an overestimation of the CMM effectiveness of treatment when compared to SCS in patients with CRPS. Estimating cost-effectiveness of SCS for CRPS is speculative because there are no primary cost data available. More research in CRPS patients, specifically economic evaluations alongside RCTs for SCS is needed.

Table 43 shows a comparison between the results obtained by ABHI and ScHARR models. In both FBSS indications (CMM alone and reoperation), the main differences appear to be in the costs. This is because the ABHI model uses estimated costs obtained from the PROCESS trial (in academic confidence) and ScHARR uses estimated costs obtained from other sources as outlined in Independent economic assessment by ScHARR. In CRPS the main differences appear to be in both parameter costs and QALYs. This is the result of the different estimated costs used in the models and the difference in the utility values input in each model as outlined in Independent economic assessment by ScHARR.

Ischaemic pain model summary of key results

It is difficult to determine whether SCS intervention represents value for money when there is not enough evidence to demonstrate its comparative efficacy. The threshold analysis suggests that the most favourable economic profiles for treatment with SCS are when compared to CABG in patients clinically appropriate to receive PCI and in patients clinically appropriate to receive CABG and PCI. In these two cases, if efficacy is equivalent, SCS would dominate (cost less and accrued more survival benefits) CABG.

The threshold analysis suggests that for patients clinically appropriate for CABG to achieve £20,000 per LYG, SCS should provide 0.0235 LYG (around 8.5 days) when compared to CABG. SCS should provide 0.0155 LYG (around 5.58 days) to achieve £30,000 per LYG. SCS should provide 0.185 and 0.125 LYG (around 66.6 days and 45 days) over PCI treatment to achieve £20,000 and £30,000 per LYG. When compared to CMM, SCS should provide 0.35 and 0.23 LYG (around 126 days and 82.8 days) to achieve £20,000 and £30,000 per LYG.

For patients appropriate for CABG, to achieve a cost per QALY gained of £20,000 or less, expected utility value in the SCS intervention must be at least 0.6218 when compared with CABG, at least 0.6001 when compared with PCI and at least 0.6321 when compared with CMM. For ICERs of £30,000 QALY gained or less, the expected utility

TABLE 43 *Results comparison between ABHI and ScHARR models*

	ABHI model			**ScHARR model**		
50% pain threshold criteria	**Cost difference**	**QALYs difference**	**ICER**	**Cost difference**	**QALYs difference**	**ICER**
Device longevity						
FBSS: SCS + CMM vs CMM alone						
Base case: 4 years	£11,439	1.25	£9155	£10,035	1.26	£7996
2 years			£30,285			£26,755
7 years			£2745			£2304
> 7 years			SCS + CMM dominates			SCS + CMM dominates
FBSS: SCS + CMM vs reoperation						
Base case: 4 years	£10,651	1.34	£7954	£9430	1.34	£7043
2 years			£26,445			£23,536
7 years			£2362			£2055
> 7 years			SCS + CMM dominates			SCS + CMM dominates
CRPS: SCS + CMM vs CMM alone						
Base case: 4 years	£12,041	0.64	£18,881	£8775	0.35	£25,095
2 years			£52,541			£80,388
7 years			£8737			£8591
> 7 years			SCS + CMM dominates			SCS + CMM dominates

value must be at least 0.6203 when compared with CABG, at least 0.5884 when compared with PCI and at least 0.6103 when compared with CMM.

For patients appropriate for CABG and PCI, to achieve a cost per QALY gained of £20,000 or less, expected utility value in the SCS intervention must be at least 0.5687 when compared with PCI and at least 0.5657 when compared with CMM. For ICERs of £30,000 QALY gained or less, the expected utility value must be at least 0.5624 when compared with PCI, at least 0.5657 when compared with CMM.

It should be restated that because of the dearth of published evidence concerning utility values and expected survival for SCS in the treatment of refractory angina, the results of this health economic model should be carefully interpreted.

Budget impact analysis

This section presents estimates of the budget impact of a positive recommendation for each indication; FBSS, CRPS and refractory angina (RA). The projected usage of SCS implant is presented over a 6-year period. According to the Hospital Episode Statistics, an estimated 639 patients received an SCS implant in England in 2006.[54] It is assumed that the same number received an implant in year 2007. *Table 44* presents the percentage of SCS implants used for each indication with 5% year-on-year growth and a 4-year device longevity. This indication split was based on breakdown of activity within an existing chronic pain management unit at the James Cook University Hospital, Middlesbrough (Dr S. Eldabe, Consultant in Anaesthesia and Pain, James Cook University Hospital, Middlesborough, personal communication).

The estimated budget impact for SCS treatment of FBSS, CRPS and refractory angina is presented in *Table 45*.

The reduction in costs in FBSS from year 1 to year 2 is the result of cost savings of those patients that had an implant at year 1 (£1622 of cost savings). Nevertheless, year 2 also considers those patients

TABLE 44 *Projected usage of SCS with a 5% year-on-year growth*

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	Split		**5%**	**10%**	**15%**	**20%**	**25%**
FBSS	45%	288	302	332	382	458	573
CRPS	32%	204	215	236	272	326	407
RA	9%	58	60	66	76	92	115
CLI	5%	32	34	37	42	51	64
Other	9%	58	60	66	76	92	115
	Total	639	671	738	849	1019	1273

RA, refractory angina.

TABLE 45 *Budget impact estimates*

Indication	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
FBSS	£2,660,700	£2,304,009	£2,022,944	£1,767,992	£4,687,758	£5,105,178
CRPS	£1,571,633	£1,379,688	£1,235,192	£1,111,933	£2,818,236	£3,105,617
Angina						£797,602

receiving a first-time SCS implant. This pattern is repeated until year 4. The cost increase at year 5 is the result of having a battery replacement when assuming a 4-year device longevity. Therefore, the cost of treating FBSS with SCS versus CMM is projected to be approximately £5.1 million at year 6. The cost of treating CRPS with SCS is projected to be £3.1 million and the cost of treating angina with SCS is projected to be approximately £800,000.

Chapter 5

Assessment of factors relevant to the NHS and other parties

For the patient, chronic pain is an important cause of physical and emotional suffering.

Chronic pain can be disabling and lead to work absenteeism, or it may require giving up work, or a job change or change of job responsibility.[123] Inability to work impacts society through the payment of disability benefits. With an ageing population, chronic pain may be becoming more prevalent.

Patients with cognitive impairment may be considered incapable of operating a SCS device. According to the British Pain Society, cognitive impairment is not a contraindication, but the patient must have a cognisant carer and adequate social support.[35]

With regard to measurement of disease, pain measurement with the visual analogue scale (VAS) would be unsuitable for patients with sight problems. For these patients, the verbal rating scale (VRS) could be used instead.[124] Many measures of health-related quality of life have been validated translated into languages other than English, which could be relevant to patients for whom English is not their first language.[29,30,125–127]

Pain management can involve a multidisciplinary team. SCS requires trained surgeons. After implantation, follow-up visits are required for monitoring patients. Patients with complications may require further surgery.

Chapter 6
Discussion

Statement of principal findings

Clinical effectiveness data were available from 11 RCTs, three of which concerned neuropathic pain (FBSS and CRPS type I), and eight ischaemic pain (CLI and angina). Comparator treatments employed by trials were relevant to UK practice. Complication rates varied across trials, but were usually minor.

Good quality (in terms of adequate randomisation and allocation concealment, and reporting intention-to-treat analysis), adequately powered trials were available for the neuropathic conditions FBSS and CRPS type I. Trial evidence reported that SCS was significantly more effective than CMM in reducing neuropathic pain of FBSS or CRPS. The SCS was superior to CMM in improving HRQoL in FBSS, though not in CRPS. A trial of lower quality found SCS to be more effective in reducing pain than reoperation for FBSS.

Most of the ischaemic pain trials were statistically underpowered and of lower quality than the neuropathic pain trials. One good-quality CLI trial reported that SCS was more effective than CMM in reducing analgesic use at up to 6 months, although not at 18 months. No other measures differed significantly between groups, although there was a non-significant trend for a subgroup of patients with intermediate skin microcirculation before treatment to favour SCS for amputation rate. Other CLI trials found that SCS was no more effective than CMM for pain relief, limb survival or HRQoL.

One of the eight ischaemic pain trials was adequately powered, and suggested that, in angina, SCS was more effective than percutaneous myocardial revascularisation (PMR; at 3 months, but not at 12 months) for increasing time to angina, though SCS and PMR were of similar effectiveness for HRQoL. Short-term follow-up data (6–8 weeks) suggested that SCS was more effective than no SCS or an inactive device in delaying the onset of angina pain during exercise or in reducing nitrate consumption. SCS was of equal or lower effectiveness than CABG, although exercise testing was completed with the SCS device switched off.

Populations in trials had previously had inadequate pain relief from other therapies, and in some cases were ineligible for potentially useful surgical therapies. This implies that any pain relief that could be provided would be of clinical benefit to patients, and this need not be as much as a 50% reduction of baseline pain.

The results generated are sensitive to changes in the device longevity, device average price and costs of CMM. The majority of results are governed by the costs of the treatment strategies being compared. The analyses demonstrate that SCS for patients with FBSS (compared to CMM and reoperation) is a cost-effective intervention. In the CRPS indication the incremental cost-effectiveness ratios obtained tend to be higher, and in some cases above £30,000 per QALY. This is linked to the RCT data used to model SCS clinical effectiveness. The RCT compared SCS to a physical therapy that is different to the therapy given to National Health Service patients. Further research is required to allow more precise estimates to be calculated in the analysis of CRPS clinical effectiveness.

Strengths and limitations of the assessment

Strengths

The literature search was comprehensive. All included trials used SCS in line with CE-marked indications, and all trial comparators are currently used in the UK, making all the included trials of relevance to UK practice. Results are consistent with other reviews of SCS. A mathematical model was constructed that allowed the analysis of the impact of short-term and long-term clinical effectiveness over cost and benefits for SCS compared with CMM or reoperation in patients with neuropathic pain. It was shown that SCS can be cost-effective for FBSS and CRPS type I.

Limitations

We do not know if there were relevant trials that were not published in English and, if there were, whether including such studies would have altered the results. Since the searches and review were completed, 5-year results of the included CRPS trial have been published in full, rather than in the letter that was included in the review.[128] However, this does not alter the 5-year result that was reported in the review. A number of conservative assumptions were made. Some assumptions were made with respect to the clinical effectiveness of SCS in patients with CRPS type I, because of the data obtained in the RCT. It was also assumed that there were no complications associated with CMM. The RCTs data for modelling angina did not provide usable HRQoL. The published evidence of clinical effectiveness of SCS in the treatment of CLI showed that there was no significant difference between groups in terms of pain relief, for SCS versus CMM or analgesic treatment. Therefore, the cost-effectiveness of SCS in refractory angina and CLI patients is unknown.

Uncertainties

It is unclear how much the clinical effectiveness of SCS in FBSS and CRPS can be generalised to other neuropathic pain conditions. It is unclear whether the positive findings from case series on other neuropathic conditions would be demonstrated in RCTs.

The major uncertainties in this assessment relate to the probability of achieving optimal pain relief in the SCS arm relative to the comparator arm. This has a major influence on the cost-effectiveness ratios. The length of benefits in the SCS arm relative to the comparator arm can also add uncertainty in terms of the overall cost-effectiveness estimates. This has a major influence of the cost-effectiveness ratio, specifically on the CRPS indication.

Considerable variation is present in two parameters of the study, device longevity and device cost. These parameters have major influences on the cost-effectiveness estimates determining whether the SCS arm is dominant or cost-effective.

The model assumes that the degradation in pain relief in the SCS arm is the result of device withdrawal and not of a parameter defined as tolerance (gradual loss of pain control even when the system is fully functional). There is no evidence to support the aetiology of this phenomenon in relation to the plasticity of central pain-processing systems.

Chapter 7
Conclusions

Implications for service provision

It should be considered during the interpretation of the review findings that the availability of clinical effectiveness data to inform the cost-effectiveness modelling was limited for CRPS and angina. For FBSS the clinical effectiveness data were obtained from two company-sponsored RCTs and therefore there is risk of bias.

Conclusions on the cost-effectiveness of spinal cord stimulation in treatment of neuropathic pain

This analysis suggests that in patients with FBSS who have an inadequate response to medical or surgical treatment, the estimated SCS incremental cost-effectiveness ratios are below £20,000 per QALY gained.

The cost-effectiveness results suggest that at base case (15-year time horizon and a 4-year device longevity) for FBSS, SCS + CMM has a cost per QALY of £7996 (£5845 to £14,215) compared with CMM alone. When the device longevity is 8 or more years SCS + CMM is expected to dominate CMM. The cost-effectiveness results suggest that at base case for FBSS, SCS + CMM has a cost per QALY of £7043 (£5562 to £11,006) compared with reoperation. SCS + CMM is expected to dominate reoperation for a device longevity of at least 8 years. In CRPS, the cost-effectiveness estimates suggest that at base case SCS + CMM has a cost per QALY of £25,095 (£11,379 to £32,814) compared with CMM alone. When the device longevity is 8 or more years SCS + CMM is expected to dominate CMM.

The sensitivity analyses demonstrate that the results are highly sensitive to the device cost and device longevity.

Conclusions on the cost-effectiveness of SCS in treatment of ischaemic pain

The threshold analysis suggests that the most favourable economic profiles for treatment with SCS are when compared to coronary artery bypass grafting (CABG) in patients clinically appropriate to receive percutaneous coronary intervention (PCI) and in patients clinically appropriate to receive CABG and PCI.

The threshold analysis suggests that for patients clinically appropriate for CABG to achieve £20,000 per LYG, SCS should provide 0.0235 LYG (around 8.5 days) when compared with CABG. SCS should provide 0.0155 LYG (around 5.58 days) to achieve £30,000 per LYG.

Although it is difficult to determine whether SCS intervention represents value for money, the threshold analysis suggests that the incremental cost-effectiveness ratio of SCS + CMM is likely to be better than £30,000 per QALY gained for additional survival benefits that range from 5.58 to 82.8 days. These survival benefits would depend on the patients' suitability for different revascularisation and medical treatments.

Suggested research priorities

There is a need for RCTs in other types of chronic neuropathic pain, such as phantom limb pain or peripheral neuralgia. For ischaemic pain, there is a need for trials with larger populations. RCTs of critical limb ischaemia subgroups (intermediate skin microcirculation, adequate transcutaneous oxygen pressure, pain relief and paraesthesia coverage in response to test stimulation, patients without arterial hypertension) could indicate potentially useful selection criteria for SCS.

Trials are needed with longer follow-up periods; there is currently a notable lack of long-term follow-up in the case of angina. There is no good way to blind patients in SCS trials. Sham stimulation does not work because patients are aware of paraesthesia, although excluding patients who have previously used SCS may limit bias from expectations of stimulation. There can be a strong placebo effect from surgery, but the placebo effect dwindles over time, and so long follow-up trials go some way to addressing this.

The use of validated health-related quality of life and pain measures is to be recommended. Trials using exercise training to assess outcomes may be more valid with SCS switched on during measurement. Trials by independent researchers without a commercial interest are needed.

Some forms of chronic pain (such as some nerve disorders) have low prevalence rates, making recruitment to RCTs difficult. Multicentre collaboration may enable adequate samples for RCTS, or other forms of data collection may be necessary. The British Pain Society recommends that centres that implant SCS devices should audit their SCS activity and encourage networking.[35] Clinicians working with SCS are currently trying to set up a national registry of SCS patients (Dr S. Eldabe, Consultant in Anaesthesia and Pain Management, James Cook University Hospital, Middlesbrough, Mr P. Eldridge, Consultant Neurosurgeon, Walton Centre for Neurology and Neurosurgery, Liverpool, Mr B. Simpson, Consultant Neurosurgeon, University Hospital of Wales Cardiff and Dr S. J. Thomson, Consultant in Pain Medicine and Anaesthesia, Basildon and Thurrock University Hospitals NHS Foundation Trust, Essex, personal communication). Although providing a research dataset would not be its primary function, such a registry has the potential to be useful for research, defining research questions for definitive prospective examination. The data collected could be particularly valuable if follow-up of patients across all centres included the same clearly defined outcome measures. Registries can provide prospectively collected data for later retrospective studies, and although such database studies are more prone to bias than RCTs, they provide access to larger patient cohorts, which is beneficial when many of the current studies are statistically underpowered.

Acknowledgements

About ScHARR

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NIHR to facilitate high-quality health services research and capacity development.

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Acknowledgements

Clinical advisors

Dr S. Eldabe, Consultant in Anaesthesia and Pain Management, James Cook University Hospital Middlesbrough

Mr P. Eldridge, Consultant Neurosurgeon, Walton Centre for Neurology and Neurosurgery Liverpool

Mr B. Simpson, Consultant Neurosurgeon, University Hospital of Wales Cardiff

Dr S. J. Thomson, Consultant in Pain Medicine and Anaesthesia, Basildon and Thurrock University Hospitals NHS Foundation Trust Essex

The authors also wish to thank Gill Rooney for her help in preparing and formatting the report and M. Lloyd-Jones for input into the scoping workshop for the project. The authors are grateful to Mr S. Dixon, ScHARR, Dr B. Collett, Leicester Royal Infirmary, Dr C. Stannard, Consultant in Pain Medicine Bristol, and Dr I. Bradbury, Queen's University Belfast, for providing feedback on the draft version of the report.

Contribution of authors

E. L. Simpson conducted the clinical effectiveness review, A. Duenas and J. Chilcott conducted the cost-effectiveness review, D. Papaioannou conducted the literature searches. All the authors were involved in preparing the protocol for the report. Jim Chilcott and Eva Kaltenthaler are guarantors.

References

1. Association for the Study of Pain. Classification of chronic pain. *Pain* 1986;Suppl 3:S1–S226.

2. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet* 1999;**354**:1248–52.

3. Ashburn MA, Staats PS. Management of chronic pain. *Lancet* 1999;**353**:1865–9.

4. Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms. Seattle: I*ASP Press;* 1994.

5. Taylor RS. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. *J Pain Symptom Manage* 2006;**31**:S13–S19.

6. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, *et al*. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;**33** Suppl.1:S5–S67.

7. European Working Group on Critical Limb Ischaemia. Second European consensus document on chronic critical leg ischaemia. *Circulation* 1991;**84** Suppl.:1–26.

8. ACC/AHA. 2002 guideline update for the management of patients with chronic stable angina – summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 2002;**41**:159–68.

9. The Criteria Committee of the New York Heart Asociation. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th edn. Boston: Brown & co.;1994. p.253–6.

10. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 1981;**64**:1227–34.

11. Neuropathic Pain Network. http://www.neuropathicpainnetwork.org/english/index.asp; 2004. Accessed 8 February 2008.

12. Torrance N, Smith BH, Bennett M, Lee AJ. The epidemiology of chronic neuropathic pain in the community. Results from a general population survey. *J Pain* 2006;**7**:281–9.

13. Jensen SA, Vatten LJ, Myhre HO. The prevalence of chronic critical lower limb ischaemia in a population of 20,000 subjects 40–69 years of age. *Eur J Vasc Endovasc Surg* 2006;**32**:60–5.

14. Shaper AG, Cook DG, Walker M, Macfarlane PW. Prevalence of ischaemic heart disease in middle aged British men. *Br Heart J* 1984;**51**:595–605.

15. Breivik H, Collet B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006;**10**:287–333.

16. McDermott A, Toelle TR, Rowbotham DJ, Schefer CP, Dukes E. The burden of neuropathic pain: results from a cross-sectional survey. *Eur J Pain* 2006;**10**:127–35.

17. Goodacre S, Nicholl J, Dixon S, Cross E, Angelini K, Arnold J, *et al*. Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ* 2004;**328**:257.

18. Tengs TO, Lin TH. A meta-analysis of quality of life estimates for stroke. *Pharmacoeconomics* 2003;**21**:191–200.

19. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. *Pain* 1983;**16**:87–101.

20. Carlsson AM. Assessment of chronic pain. II. Problems in the selection of relevant questionnaire items for classification of pain and evaluation and prediction of therapeutic effects. *Pain* 1984;**19**:173–84.

21. Cruccu G, Simpson BA, Taylor RS. 56 EFNS guidelines on spinal cord stimulation for neuropathic pain. *Eur J Pain* 2007;**11**:22.

22. Attal N, Cruccu G, Haanpaa M. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;**13**:1153–69.

23. Farrar JT, Young JP Jr, LaMoreaux L. Clinical importance of change in chronic pain intensity

measured on an 11-point numerical pain rating scale. *Pain* 2001;**94**:149–58.

24. Melzack, R. Prolonged relief of pain by brief, intense transcutaneous somatic stimulation. *Pain* 1975;**1**:357–73.

25. Hunt SM, McKenna SP, McEwen J, Williams J, Papp E. The Nottingham Health Profile: subjective health status and medical consultations. *Soc Sci Med* 1981;15A:221–9.

26. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. *J R Coll Gen Pract* 1985;**35**:185–188.

27. Jenkinson C, Fitzpatrick R. Measurement of health status in patients with chronic illness: comparison of the Nottingham Health Profile and the General Health Questionnaire. *Fam Pract* 1990;**7**:121–4.

28. Jenkinson C, Fitzpatrick R, Argyle M. The Nottingham Health Profile: an analysis of its sensitivity in differentiating illness groups. *Soc Sci Med* 1988;**27**:1411–14.

29. The Euroqol Group. Euroqol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–208.

30. de Bruin AF, Diederiks JPM, de Witte LP, Stevens FCJ, Philipsen H. The development of a short generic version of the Sickness Impact Profile. *J Clin Epidemiol* 1994;**47**:407–18.

31. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.

32. Brazier J, Harper R. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992;**305**:160–4.

33. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, *et al*. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol* 1995;**25**:333–41.

34. Marquis P, Fayol C, Joire JE. Clinical validation of a quality of life questionnaire in angina pectoris patients. *Eur Heart J* 1995;**16**:1554–60.

35. British Pain Society and Society of British Neurological Surgeons. Spinal cord stimulation for the management of pain: recommendations for best clinical practice. London: British Pain Society; 2005.

36. National Statistics. www.statistics.gov.uk/cci/nugget.asp?id=6. Accessed 15 January 2008.

37. Taylor RS. Epidemiology of refractory neuropathic pain. *Pain Pract* 2006;**6**:22–26.

38. British Heart Foundation. www.heartstats.org/datapage.asp?id=122. Accessed 15 January 2008.

39. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, Eliasson T, *et al*. The problem of chronic refractory angina: report from the ESC Joint Study Group on the Treatment of Refractory Angina. *Eur Heart J* 2002;**23**:355–70.

40. Beard J. ABC of arterial and venous disease: chronic lower limb ischaemia. *BMJ* 2000;**320**:854–7.

41. North RB, Shipley J. Practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain. *Pain Med* 2007;**8**:S200–S275.

42. Department of Health. The National Service Framework for long-term conditions. London: Department of Health; 2005.

43. The Royal College of Anaesthetists and The Pain Society (The British Chapter of the International Association for the Study of Pain). Pain management services good practice. London: Royal College of Anaesthetists and The Pain Society; 2003.

44. British Pain Society and Royal College of General Practitioners. A practical guide to the provision of chronic pain services for adults in primary care. London: British Pain Society and Royal College of General Practitioners; 2004.

45. NHS Quality Improvement Scotland. Management of chronic pain in adults. Edinburgh: NHS Quality Improvement Scotland; 2007.

46. International Association for the Study of Pain. Desirable characteristics for pain treatment facilities. Seattle: IASP Press; 2006.

47. Middleton P, Simpson B, Maddern G. Spinal cord stimulation/neurostimulation: an accelerated systematic review. ASERNIP-S Report No. 43. Adelaide, South Australia: ASERNIP-S; 2003.

48. Cameron, T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg* 2004;**100**:254–67.

49. Taylor RS, Van Buyten J, Buchser E. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. *Spine* 2005;**30**:152–60.

50. Grabow TS, Tella PK, Raja SN. Spinal cord stimulation for complex regional pain syndrome: an evidence-based medicine review of the literature. *Clin J Pain* 2003;**19**:371–83.

51. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *Eur J Pain* 2006;**10**:91–101.

52. Turner JA, Loeser JD, Bell KG. Spinal cord stimulation for chronic low back pain: a systematic literature synthesis. *Neurosurgery* 1995;**37**:1088–95.

53. The Information Centre (England). Hospital Episode Statistics – 2005–06. Leeds: The NHS Information Centre; 2007.

54. The Information Centre (England). Hospital Episode Statistics – 2006–07. Leeds: The NHS Information Centre; 2008.

55. Neuromodulation Society of UK and Ireland. Submission to NICE for the Health Technology Appraisal of *Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin*. 2008.

56. Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews. CRD Report 4, 2nd edn. York: Centre for Reviews and Dissemination; 2001.

57. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ* 1998;**317**:1185–90.

58. Spincemaille GHK. Spinal cord stimulation in patients with critical limb ischemia: a preliminary evaluation of a multicentre trial. *Acta Chirurg Aust* 2000;**32**:49–51.

59. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, *et al.* Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007;**132**:179–88.

60. Kumar K, North R, Taylor R, Sculpher M, Van den Abeele C, Gehring M, *et al*. Spinal cord stimulation vs. conventional medical management: a prospective, randomized, controlled, multicenter study of patients with failed back surgery syndrome (PROCESS study). *Neuromodulation* 2005;**8**:213–18.

61. Milbouw G, Leruth S. Spinal cord stimulation vs conventional medical management: a multicenter randomized controlled trial of patients with failed back surgery syndrome (PROCESS study). *Surg Neurol* 2007;**68**:201.

62. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery* 2005;**56**:98–106.

63. North RB, Kidd DH, Piantadosi S. Spinal cord stimulation versus reoperation for failed back surgery syndrome: a prospective, randomized study design. *Acta Neurochirurg Suppl* 1995;**64**:106–8.

64. North RB, Kidd DH, Lee MS, Piantodosi S. A prospective, randomized study of spinal cord stimulation versus reoperation for failed back surgery syndrome: initial results. *Stereotac Funct Neurosurg* 1994;**62**:267–72.

65. Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, *et al*. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000;**343**:618–24.

66. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Spinal cord stimulation for chronic reflex sympathetic dystrophy – five-year follow-up. *N Engl J Med* 2006;**354**:2394–6.

67. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* 2004;**55**:13–18.

68. Spincemaille GH, Klomp HM, Steyerberg EW, Habbema JD. Pain and quality of life in patients with critical limb ischaemia: results of a randomized controlled multicentre study on the effect of spinal cord stimulation. ESES study group. *Eur J Pain* 2000;**4**:173–84.

69. Spincemaille GH, Klomp HM, Steyerberg EW, van Urk H, Habbema JD, ESES Study Group. Technical data and complications of spinal cord stimulation: data from a randomized trial on critical limb ischemia. *Stereotac Funct Neurosurg* 2000;**74**:63–72.

70. Klomp HM, Spincemaille GH, Steyerberg EW, Habbema JD, van Urk H. Spinal-cord stimulation in critical limb ischaemia: a randomised trial. ESES Study Group. *Lancet* 1999;**353**:1040–4.

71. Ubbink DT, Spincemaille GH, Prins MH, Reneman RS, Jacobs MJ. Microcirculatory investigations to determine the effect of spinal cord stimulation for critical leg ischemia: the Dutch multicenter randomized controlled trial. *J Vasc Surg* 1999;**30**:236–44.

72. Klomp HM, Spincemaille GH, Steyerberg EW, Berger MY, Habbema JD, van Urk H. Design issues of a randomised controlled clinical trial on spinal cord stimulation in critical limb ischaemia. *Eur J Vasc Endovasc Surg* 1995;**10**:478–85.

73. Suy R, Gybels J, van Damme H, Martin D, van Maele R, Delaporte C. Spinal cord stimulation for ischemic rest pain. The Belgian randomized study. In Horsch S, Clayes L, editors. *Spinal cord stimulation: an innovative method in the treatment of PVD*. Darmstadt: Steinkopff; 1994. pp.197–202.

74. Jivegard LE, Augustinsson LE, Holm J, Risberg B, Ortenwall P. Effects of spinal cord stimulation (SCS) in patients with inoperable severe lower limb ischaemia: a prospective randomised controlled study. *Eur J Vasc Endovasc Surg* 1995;**9**:421–5.

75. Claeys LG, Horsch S. Transcutaneous oxygen pressure as predictive parameter for ulcer healing in endstage vascular patients treated with spinal cord stimulation. *Int Angiol* 1996;**15**:344–9.

76. Claeys LGY, Horsch S. Spinal cord stimulation (SCS) following intravenous prostaglandin El (PGE1) therapy in non-reconstructible peripheral vascular disease (PVD): Fontaine stage IV. *Pain Clin* 1999;**11**:235–43.

77. Claeys L, Horsch S. Effects of spinal cord stimulation on ischaemic inflammatory pain and wound healing in patients with peripheral arterial occlusive disease. *Pain Digest* 1997;**7**:200–3.

78. Claeys LGY. Epidural spinal cord stimulation following intravenous prostaglandin E1 therapy in patients with ischaemic pain (peripheral vascular disease Fontaine stage IV). Preliminary results of a controlled randomized study. *Pain Clin* 1998;**10**:165–172.

79. De Jongste MJ, Hautvast RW, Hillege HL, Lie KI. Efficacy of spinal cord stimulation as adjuvant therapy for intractable angina pectoris: a prospective, randomized clinical study. Working Group on Neurocardiology. *J Am Coll Cardiol* 1994;**23**:1592–7.

80. Mannheimer C, Eliasson T, Augustinsson LE, Blomstrand C, Emanuelsson H, Larsson S, *et al*. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY study. *Circulation* 1998;**97**:1157–63.

81. Norrsell H, Pilhall M, Eliasson T, Mannheimer C. Effects of spinal cord stimulation and coronary artery bypass grafting on myocardial ischemia and heart rate variability: further results from the ESBY study. *Cardiology* 2000;**94**:12–18.

82. Ekre O, Eliasson T, Norrsell H, Wahrborg P, Mannheimer C, Electrical Stimulation versus Coronary Artery Bypass Surgery in Severe Angina Pectoris. Long-term effects of spinal cord stimulation and coronary artery bypass grafting on quality of life and survival in the ESBY study. [see comment]. *Eur Heart J* 2002;**23**:1938–45.

83. McNab D, Khan SN, Sharples LD, Ryan JY, Freeman C, Caine N, *et al*. An open label, single-centre, randomized trial of spinal cord stimulation vs. percutaneous myocardial laser revascularization in patients with refractory angina pectoris: the SPiRiT trial. *Eur Heart J* 2006;**27**:1048–53.

84. Hautvast RW, DeJongste MJ, Staal MJ, van Gilst WH, Lie KI. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. *Am Heart J* 1998;**136**:1114–20.

85. Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. *Cochrane Database Syst Rev* 2004;CD003783.

86. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain* 2004;**108**:137–47.

87. Ubbink DT, Vermeulen H, Spincemaille GH, Gersbach PA, Berg P, Amann W. Systematic review and meta-analysis of controlled trials assessing spinal cord stimulation for inoperable critical leg ischaemia. *Br J Surg* 2004;**91**:948–55.

88. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. [update of *Cochrane Database Syst Rev* 2003;CD004001; PMID: 12917998]. *Cochrane Database Syst Rev* 2005;CD004001.

89. Turner JA, Deyo RA, Loeser JD. Spinal cord stimulation: stimulating questions. *Pain* 2007;**132**:10–11.

90. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;**1**:277–99.

91. Steedman SM, Middaugh SJ, Kee WG, Carson DS, Harden RN, Miller C. Chronic-pain medications: equivalence levels and method of quantifying usage. *Clin J Pain* 1992;**8**:201–14.

92. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. *Arch Phys Med Rehab* 1969;**50**:311–19.

93. Kemler MA, De Vet HCW. An objective and standardized test for foot function: normative values and validation in patients with reflex sympathetic dystrophy. *Arch Phys Med Rehab* 2000;**81**:1401–07.

94. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine* 2000;**25**:2940–52.

95. Hill J, Timmis A. Exercise tolerance testing. *BMJ* 2002;**324**:1084–7.

96. Andrews FM, Withey SB. Social indicators of well-being. New York: Plenum Press; 1976.

97. Zung WWK. A self-rating depression scale. *Arch Gen Psychiatry* 1965;**12**:63–70.

98. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.

99. Klomp HM, Steyerberg EW, van Urk H, Habbema JD, and ESES Study Group. Spinal cord stimulation is not cost-effective for non-surgical management of critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2006;**31**:500–8.

100. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. *J Am Med Assoc* 1994;**271**:1609–14.

101. Amann W. Spinal cord stimulation in the treatment of non-reconstructable stable critical leg ischaemia: results of the European Peripheral Vascular Disease Outcome Study (SCS-EPOS). *Eur J Vasc Endovasc Surg* 2003;**26**:280–6.

102. Ubbink DT, Vermeulen H. Spinal cord stimulation for critical leg ischemia: a review of effectiveness and optimal patient selection. *J Pain Sympt Manage* 2006;**31**(Suppl.4):S30–S35.

103. Mannheimer C, Eliasson T, Andersson B, Bergh CH, Augustinsson LE, Emanuelsson H, *et al*. Effects of spinal cord stimulation in angina pectoris induced by pacing and possible mechanisms of action. *BMJ* 1993;**307**:477–80.

104. Drummond M, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83.

105. Eddy DM. Technology assesment: The role of mathematical modelling. In Mostellar F, editor. *Assessing medical technology*. Washington: National Academy Press; 1985;144–54.

106. Organisation for Economic Co-operation and Development. Purchasing Power Parities. Paris: *OECD;* 2008.

107. Curtis L, Netten A. A unit costs of health and social care. Canterbury: *PSSRU;* 2007.

108. Taylor RJ, Taylor RS. Spinal cord stimulation for failed back surgery syndrome: a decision-analytic model and cost-effectiveness analysis. *Int J Technol Assess Hlth Care* 2005;**21**:351–8.

109. National Institute for Clinical Excellence Guidelines for manufacturers and sponsors. London: NICE; 2001.

110. National Institute for Clinical Excellence Guide to the methods of technology appraisal (reference no. 515). London: *NICE;* 2008.

111. Kumar K, Malik S, Demeria D. Treatment of chronic pain with spinal cord stimulation versus alternative therapies: cost-effectiveness analysis. *Neurosurgery* 2002;**51**:106–15.

112. Department of Health. National Tariff; 2007/08. London: *Department of Health* 2007.

113. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery* 2006;**58**:481–96.

114. Fritzell P, Hagg O, Wessberg P, Nordwall A. 2001 Volvo Award Winner in Clinical Studies: lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. *Spine* 2001;**26**:2521–34.

115. Livshits A, Rappaport ZH, Livshits V, Gepstein R. Surgical treatment of painful spasticity after spinal cord injury. *Spinal Cord* 2002;**40**:161–6.

116. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary (BNF)*. No. 54, September 2007. London: BMA and RPS; 2007.

117. Kumar K, Wilson JR, Taylor RS, Gupta S. Complications of spinal cord stimulation, suggestions to improve outcome, and financial impact. *J Neurosurg Spine* 2006;**5**:191–203.

118. Department of Health. National schedule of reference costs 2006–07. London: *Department of Health;* 2008.

119. Ratcliffe J, Thomas KJ, MacPherson H, Brazier J. A randomised controlled trial of acupuncture care for persistent low back pain: cost effectivenes analysis. *BMJ* 2006;**333**:626.

120. Griffin SC, Barber JA, Manca A, Sculpher MJ, Thompson SG, Buxton MJ, *et al*. Cost effectiveness of clinically appropriate decisions on alternative treatments for angina pectoris: prospective observational study. *BMJ* 2007;**354**:624.

121. Bernstein SJ, Laouri M, Hilborne LH, Leape LL, Kahan JO, Park RE, *et al*. Coronary angiography: a literature review and ratings of appropriateness and necessity. *Santa Monica, CA: RAND;* 1992.

122. Kemler MA, Barendse GAM, Van Kleef M, de Vet HCW, Rijks CPM, Furnee CA, Van Den Wildenberg FAJM. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000;**343**:618–24.

123. Breivik H. Chronic pain and the sympathetic nervous system. *Acta Anaesthesiol Scand* 1997;Suppl. **110**:131–4.

124. Cork RC, Isaac I, Elsharydah A, Alexander L. A comparison of the verbal rating scale and the visual analog scale for pain assessment. *Internet J Anesthesiol* 2004; 8.URL: www.ispub.com/ostia/index.php?xmlFilePath=journals/ija/vol8n1/vrs.xml

125. Erdman RAM, Passchier J, Kooijman M, Stronks DL. The Dutch version of the Nottingham Health Profile: investigations of psychometric aspects. *Psychol Rep* 1993;**72**:1027–35.

126. van Eijk JTM, Smits A, Meyboom W, Mokkink H, van Son J. Reliability and validity of the Nottingham Health Profile in the Dutch situation (internal report). Nijmegan: NUHI; 1987.

127. de Bruin AF, Buys M, de Witte LP, Diederiks JPM. The Sickness Impact Profile: SIP68, a short generic version: first evaluation of the reliability and reproducibility. *J Clin Epidemiol* 1994;**47**:863–71.

128. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, Van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg* 2008;**108**:292.

129. Manufacturer submission to NICE – Cross industry submission by the Association of British Healthcare Industries on behalf of Advanced Neuromodulation Systems (a division of St Jude Medical Ltd), Boston Scientific Ltd, and Medtronic Ltd. 2008.

130. De Jongste MJ, Staal MJ. Preliminary results of a randomized study on the clinical efficacy of spinal cord stimulation for refractory severe angina pectoris. *Acta Neurochirurg Suppl* 1993;**58**:161–4.

131. Eddicks S, Maier-Hauff K, Schenk M, Muller A, Baumann G, Theres H. Thoracic spinal cord stimulation improves functional status and relieves symptoms in patients with refractory angina pectoris: the first placebo-controlled randomised study. *Heart* 2007;**93**:585–90.

132. Di Pede F. Long-term effects of spinal cord stimulation on myocardial ischemia and heart rate variability: results of a 48-hour ambulatory electrocardiographic monitoring. *Ital Heart J* 2001;**2**:690–5.

133. Jessurun GA, DeJongste MJ, Hautvast RW, Tio RA, Brouwer J, van Lelieveld S, *et al*. Clinical follow-up after cessation of chronic electrical neuromodulation in patients with severe coronary artery disease: a prospective randomized controlled study on putative involvement of sympathetic activity. *Pacing Clin Electrophysiol* 1999;**22**:1432–9.

134. Lind G, Schechtmann G, Winter J, Meyerson BA, Linderoth B. Baclofen-enhanced spinal cord stimulation and intrathecal baclofen alone for neuropathic pain: long-term outcome of a pilot study. *Eur J Pain* 2008;**12**:132–6.

135. Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. *Lancet* 1996;**348**:1698–701.

136. Fiume D. Permanent spinal cord stimulation in patients with coronary heart disease. Preliminary data. *Acta Neurochir Wien* 1994;**129**:243–4.

Appendix 1
CE marked indications

Table 46 *Spinal cord stimulation (SCS) devices with implantable pulse generator and non-rechargeable internal battery*

Name of product	Manufacturer	CE marked indications
Synergy	Medtronic Ltd	As an aid in the management of chronic, intractable pain of the trunk and/or limbs, peripheral vascular disease, or intractable angina pectoris
Synergy Versitrel	Medtronic Ltd	As an aid in the management of chronic, intractable pain of the trunk and/or limbs, peripheral vascular disease, or intractable angina pectoris
Itrel 3	Medtronic Ltd	As an aid in the management of chronic, intractable pain of the trunk and/or limbs, peripheral vascular disease, or intractable angina pectoris
Prime ADVANCED	Medtronic Ltd	As an aid in the management of chronic pain, intractable pain of the trunk and/or limbs, peripheral vascular disease, or refractory angina pectoris
Genesis IPG (3608)	Advanced Neuromodulation Systems (a division of St Jude Medical Ltd)	As an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with any of the following: failed back surgery syndrome, and intractable low back pain and leg pain
Genesis XP (3609)	Advanced Neuromodulation Systems (a division of St Jude Medical Ltd)	As an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with any of the following: failed back surgery syndrome, and intractable low back pain and leg pain
Genesis XP Dual (3644)	Advanced Neuromodulation Systems (a division of St Jude Medical Ltd)	As an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with any of the following: failed back surgery syndrome, and intractable low back pain and leg pain
Genesis G4	Advanced Neuromodulation Systems (a division of St Jude Medical Ltd)	As an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with any of the following: failed back surgery syndrome, and intractable low back pain and leg pain

Table 47 *SCS devices with implantable pulse generator and rechargeable internal battery*

Name of product	Manufacturer	CE marked indications
Restore ADVANCED	Medtronic Ltd	As an aid in the management of chronic pain, intractable pain of the trunk and/or limbs, peripheral vascular disease, or refractory angina pectoris
Restore ULTRA	Medtronic Ltd	As an aid in the management of chronic pain, intractable pain of the trunk and/or limbs, peripheral vascular disease, or refractory angina pectoris
Precision SC-1110	Advanced Bionics (a division of Boston Scientific Ltd)	As an aid in the management of chronic intractable pain
Eon	Advanced Neuromodulation Systems (a division of St Jude Medical Ltd)	As an aid in the management of chronic intractable pain of the trunk and/or limbs

Table 48 *SCS devices with radiofrequency system*

Name of product	Manufacturer	CE marked indications
Renew (3408)	Advanced Neuromodulation Systems (a division of St Jude Medical Ltd)	As an aid in the management of chronic pain, intractable pain of the trunk and/or limbs
Renew (3416)	Advanced Neuromodulation Systems (a division of St Jude Medical Ltd)	As an aid in the management of chronic pain, intractable pain of the trunk and/or limbs
Patient selection or contraindications for devices stipulate a test stimulation for patients before permanent implant.[129]		

Appendix 2

MEDLINE search strategy

The strategy below was combined with RCTs, systematic review and economics filters.

1. chronic pain$.tw.
2. exp Low Back Pain/
3. exp Pain/
4. chronic.tw.
5. 3 and 4
6. exp Fibromyalgia/
7. neuropathic pain$.tw.
8. damaged nerve$.tw.
9. damaged nervous system$.tw.
10. exp Phantom Limb/
11. exp Complex Regional Pain Syndromes/
12. crps.tw.
13. peripheral nerve$damage$.tw.
14. peripheral vascular disease/
15. refractory angina.tw.
16. exp Brachial Plexus Neuropathies/
17. exp Radiation Injuries/
18. post-radiation.tw.
19. exp Amputation/
20. spinal surgery.tw.
21. intercostal$neuralgia.tw.
22. exp Spinal Cord Injuries/
23. nerve lesion$.tw.
24. nerve dysfunction.tw.
25. nerve damage.tw.
26. nerve pathолog$.tw.
27. nerve injur$.tw.
28. damage$nervous system.tw.
29. neurogenic pain$.tw.
30. neuropath$.tw.
31. ischaemic pain$.tw.
32. ischemic pain$.tw.
33. Pain, intractable/
34. (failed back surgery syndrome or fbss).tw.
35. peripheral neuropath$.tw.
36. stump pain.tw.
37. exp Angina pectoris/
38. (bone and pain$).tw.
39. (joint and pain$).tw.
40. neuralgia, postherpetic/
41. Radiculopathy/
42. radicular pain.tw.
43. pseudo radiculopath$.tw.
44. pseudoradiculopath$.tw.
45. radiculopath$.tw.
46. critical limb ischaemia.tw.
47. ischaemic limb pain$.tw.
48. Thromboangiitis Obliterans/
49. buerger's disease.tw.
50. buergers disease.tw.
51. buerger disease.tw.
52. vasculitide$.tw.
53. exp Polyneuropathies/
54. diabetic neuropath$.tw.
55. polyneuropath$.tw.
56. Raynaud disease/
57. Raynaud$disease.tw.
58. exp coronary vasospasm/
59. vasospas$.tw.
60. reflex sympathetic dystrophy/
61. reflex sympathetic dystroph$.tw.
62. causalgia/
63. causalgia.tw.
64. 1 or 2 or 5
65. or/6–63
66. or 65
67. exp Electric Stimulation Therapy/
68. exp Spinal Cord/
69. spinal cord stimulation$.tw.
70. scs.tw.
71. dorsal column stimulation.tw.
72. or/67–71
73. and 72

RCT filter

1. randomized controlled trial.pt
2. controlled clinical trial.pt
3. randomized controlled trials/
4. random allocation/
5. double blind method/
6. clinical trial.pt
7. exp clinical trials/
8. ((clin$adj25 trial$)).ti, ab
9. ((singl$or doubl$or trebl$or tripl$) adj25 (blind$or mask$)).ti, ab
10. placebos/
11. placebos.ti, ab
12. random.ti, ab
13. research design/
14. or/1–14

Systematic review filter

1. meta-analysis/
2. exp review literature/
3. (meta-analy$or meta analy$or metaanaly$).tw
4. meta analysis.pt
5. review academic.pt
6. review literature.pt
7. (systematic$adj3 (review$or overview$)).tw
8. letter.pt
9. review of reported cases.pt
10. historical article.pt
11. review multicase.pt
12. or/1–7
13. or/8–11
14. not 13

Economics filter

1. Economics/
2. exp "Costs and Cost Analysis"/
3. economic value of life/
4. exp economics hospital/
5. exp economics medical/
6. economics nursing/
7. exp models economic/
8. Economics, Pharmaceutical/
9. exp "Fees and Charges"/
10. exp budgets/
11. ec.fs.
12. (cost or costs or costed or costly or costing$).tw.
13. (economic$or pharmacoeconomic$or price$or pricing$).tw.
14. quality adjusted lifeyears/
15. (qaly or qaly$).af.
16. or/1–15

Strategy with quality of life filters

1. quality adjusted life year/
2. quality adjusted life.tw.
3. (qaly$or qald$or qale$or qtime$).tw.
4. disability adjusted life.tw.
5. daly$.tw.
6. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
7. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
8. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
9. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
10. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
11. (euroqol or euro qol or eq5d or eq 5d).tw.
12. (hql or hqol or h qol or hrqol or hr qol).tw.
13. (hye or hyes).tw.
14. health$year$equivalent$.tw.
15. health utilit$.tw.
16. (hui or hui1 or hui2 or hui3).tw.
17. disutili$.tw.
18. rosser.tw.
19. chronic pain$.tw.
20. exp Low Back Pain/
21. exp Pain/
22. chronic.tw.
23. and 22
24. exp Fibromyalgia/
25. neuropathic pain$.tw.
26. damaged nerve$.tw.
27. damaged nervous system$.tw.
28. exp Phantom Limb/
29. exp Complex Regional Pain Syndromes/
30. crps.tw.
31. peripheral nerve$damage$.tw.
32. peripheral vascular disease/
33. refractory angina.tw.
34. exp Brachial Plexus Neuropathies/
35. exp Radiation Injuries/
36. post-radiation.tw.
37. exp Amputation/
38. spinal surgery.tw.
39. intercostal$neuralgia.tw.
40. exp Spinal Cord Injuries/
41. nerve lesion$.tw.
42. nerve dysfunction.tw.
43. nerve damage.tw.
44. nerve pathолog$.tw.
45. nerve injur$.tw.
46. damage$nervous system.tw.
47. neurogenic pain$.tw.
48. neuropath$.tw.
49. ischaemic pain$.tw.
50. ischemic pain$.tw.
51. Pain, intractable/
52. (failed back surgery syndrome or fbss).tw.
53. peripheral neuropath$.tw.
54. stump pain.tw.
55. exp Angina pectoris/
56. (bone and pain$).tw.
57. (joint and pain$).tw.
58. neuralgia, postherpetic/
59. Radiculopathy/
60. radicular pain.tw.

61. pseudo radiculopath$.tw.
62. pseudoradiculopath$.tw.
63. radiculopath$.tw.
64. critical limb ischaemia.tw.
65. ischaemic limb pain$.tw.
66. Thromboangiitis Obliterans/
67. buerger's disease.tw.
68. buergers disease.tw.
69. buerger disease.tw.
70. vasculitide$.tw.
71. exp Polyneuropathies/
72. diabetic neuropath$.tw.
73. polyneuropath$.tw.
74. Raynaud disease/
75. Raynaud$disease.tw.
76. exp coronary vasospasm/
77. vasospas$.tw.
78. reflex sympathetic dystrophy/
79. reflex sympathetic dystroph$.tw.
80. causalgia/
81. causalgia.tw.
82. or 20 or 23
83. or/24–81
84. or 83
85. or/1–18
86. and 85

Appendix 3

Quality assessment of included trials

Critical appraisal form based on NHS CRD Report No. 4[56]

Table 49 *Quality assessment of failed back surgery syndrome trials*

Trial	PROCESS[59–61]	North[62–64]
Was the method used to assign participants to the treatment groups really random?	Yes	Yes
What method of assignment was used?	Random computer-generated blocks (of two or four) on a per site basis	Computer-generated list
Was the allocation of treatment concealed?	Yes	No (inadequate method of concealment)
What method was used to conceal treatment allocation?	Randomisation electronically locked and only accessed after patient entered the trial	Numbered, sealed, opaque envelopes provided by someone independent of trialists
Was the number of participants who were randomised stated?	Yes	Yes
Were the eligibility criteria for study entry specified?	Yes	Yes
Were details of baseline comparability presented?	Yes	No
Was baseline comparability achieved?	Mostly. Achieved for variables apart from back pain	Unclear
Was an intention-to-treat analysis included?	Yes	No (excludes patients randomised but not treated)
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Yes	No

Table 50 *Quality assessment of complex regional pain syndrome trial*

Trial	Kemler[65–67]
Was the method used to assign participants to the treatment groups really random?	Yes
What method of assignment was used?	Computer-generated table of random numbers. Stratified according to location of reflex sympathetic dystrophy (hand or foot), assigned in 2 : 1 ratio
Was the allocation of treatment concealed?	Yes
What method was used to conceal treatment allocation?	Allocation made by research assistant, by telephone, concealed from study investigators
Was the number of participants who were randomised stated?	Yes
Were the eligibility criteria for study entry specified?	Yes
Were details of baseline comparability presented?	Yes
Was baseline comparability achieved?	Yes
Was an intention-to-treat analysis included?	Yes
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Yes

Table 51 *Quality assessment of critical limb ischaemia trials*

Trial	ESES[68–72] (PILOT[58])	Suy[73]	Jivegard[74]	Claeys[75–78]
Was the method used to assign participants to the treatment groups really random?	Yes	Unclear	Unclear	Unclear
What method of assignment was used?	Random numbers table, stratified by diabetes and institution and ankle pressure	Unclear	Unclear. Stratified for sex, age, diabetes and ischaemic ulceration	Unclear
Was the allocation of treatment concealed?	Yes	Unclear	Unclear	Unclear
What method was used to conceal treatment allocation?	List held centrally in an independent research institute	Unclear	Unclear	Unclear
Was the number of participants who were randomised stated?	Yes	Yes	Yes	Yes
Were the eligibility criteria for study entry specified?	Yes	Yes	Yes	Yes
Were details of baseline comparability presented?	Yes	Yes	Yes	Yes
Was baseline comparability achieved?	Yes	Yes	Yes	Mostly. Achieved for variables apart from prior vascular leg surgeries
Was an intention-to-treat analysis included?	Yes	Yes	Yes	Yes
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Yes	Yes	Yes	Yes

Table 52 *Quality assessment of angina trials*

Trial	deJongste [79]	ESBY[80–82]	SPiRiT[83]	Hautvast[84]
Was the method used to assign participants to the treatment groups really random?	Unclear	Unclear	Yes	Unclear
What method of assignment was used?	Unclear	Unclear, not stratified	Computer-generated list, in blocks of size six and eight	Unclear, stratified by age and left ventricular ejection fraction
Was the allocation of treatment concealed?	Yes	Unclear	Yes	Unclear
What method was used to conceal treatment allocation?	Independent telephone service	Unclear	List held independently from trialists	Unclear
Was the number of participants who were randomised stated?	Yes[a]	Yes	Yes	Yes
Were the eligibility criteria for study entry specified?	Yes	Yes	Yes	Yes
Were details of baseline comparability presented?	Yes	Yes	Yes	Yes
Was baseline comparability achieved?	Yes	Mostly. Achieved for variables apart from renal disease and smoking	Yes	Mostly. Achieved for variables apart from number of myocardial infarctions and number of coronary angioplasties
Was an intention-to-treat analysis included?	Yes[a]	No (not all patients had data, but data analysed in allocated group)	No (not all patients had data, but data analysed in allocated group)	Yes
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Yes[a]	Yes	Yes	Yes

a Paper by DeJongste and Staal[130] apparently describing preliminary results of same study, has more patients ($n = 24$) randomised than reported in 1994 paper.

Appendix 4
Excluded studies

Table 53 *Excluded studies*

Reason for exclusion	Trial	Indication	Intervention (and sample size)	Comparator (and sample size)	Study period
All patients in the trial had previously had SCS (between 3–6 months). Crossover study	Eddicks *et al.*, 2007[131]	Angina	SCS [four groups with different stimulation regimens, one of which (low voltage) considered the control treatment] ($n = 12$)	(Same patients – crossovers to other study groups)	16 weeks (4 weeks in each of four different study regimens)
All patients in the trial had previously had SCS (mean 39 months). Crossover study	DiPede, 2001[132]	Angina	SCS turned on for 24 hours ($n = 15$)	(Same patients – SCS turned off for 24hrs)	48 hours
Study of withholding stimulation, No data comparing SCS on with SCS off (instead looks into the possibility of clinical rebound after withholding neurostimulation). All patients in the trial had previously had SCS (mean 42 or 34 months for treatment or control group respectively)	Jessurun *et al.*, 1999[133]	Angina	SCS turned on for 4 weeks then off for 4 weeks ($n = 12$)	SCS turned off for 4 weeks ($n = 12$)	4 weeks control, 8 weeks intervention group
All patients in the trial had previously had SCS (and had an unsatisfactory response to SCS). Not randomised	Lind *et al.*, 2008[134]	Neuropathic pain	SCS and baclofen ($n = 5$)	Intrathecal baclofen ($n = 4$)	mean 67 months
Not randomised	Amman, 2003[101]	Critical limb ischaemia	SCS (two groups: $TcPo_2 < 30$ mmHg, increased from < 10 to > 20 mmHg, and adequate pain relief and paraesthesia coverage ($n = 41$); others ($n = 32$)	No SCS ($n = 39$)	12 months
Not RCT (test stimulation of 4 days duration with random crossover design applying to this test phase only, then study is a case series)	Tesfaye *et al.*, 1996[135]	Diabetic peripheral neuropathy	SCS. Test stimulation placebo then active stimulator ($n = 5$)	SCS. Test stimulation active stimulator then placebo ($n = 5$)	2 days then crossover 2 days
No usable outcome data, not all patients had angina, no mention of pain duration	Fiume, 1994[136]	Coronary heart disease (most with angina)	SCS ($n = 13$)	No SCS ($n = 6$)	Mean follow-up 4 to 5 months

$TcPo_2$, transcutaneous oxygen pressure

Appendix 5

Data extraction tables

Appendix 5.1: Data extraction: failed back surgery syndrome

Table 54 *Failed back surgery syndrome: trial details – PROCESS*[59]

Trial name	**PROCESS**[59]
Publication type of main reference	Kumar *et al.*, 2007;[59] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Multicentre, 12 centres in Europe (UK, Belgium, Spain, Italy, Switzerland), Canada, Australia and Israel
Power calculation (priori sample calculation)	Sample size required 100 (assumed attrition rate 20%, assumed 42.5% SCS and 14.5% CMM successfully treated, groups of 40 patients each power 80% and two-tailed alpha of 0.05)
Primary aim of study	To assess the effectiveness of SCS plus CMM, compared with CMM alone
Primary study outcome	Proportion of patients achieving at least 50% pain relief in the legs
Other study outcomes	Pain VAS, medication use, Oswestry Disability Index, employment status, SF-36, patient satisfaction, complications, adverse effects
Intervention (description)	SCS and CMM (as for control group). Could request crossover at 6 months
SCS details	Test stimulation – patients experiencing at least 80% overlap of their pain with stimulation-induced paraesthesia and at least 50% leg pain relief received permanent implant. Implantable neurostimulation system, most patients Synergy system (Medtronic), three patients Itrel 3 system (Medtronic)
Comparator	CMM (could request crossover at 6 months) – at discretion of the study investigator and according to local clinical practice, included oral medications (i.e. opioid, non-steroidal anti-inflammatory drug, antidepressant, anticonvulsant or antiepileptic and other analgesics), nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care. Excluded other invasive therapy (e.g. spinal surgery, intrathecal drug delivery)

Table 55 *Failed back surgery syndrome: trial details – North*[62]

Trial name	**North**[62]
Publication type of main reference	North *et al*., 2005;[62] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, USA
Power calculation (priori sample calculation)	Sample size required 50 [to detect a significant (alpha = 0.05) difference in outcomes, with power 80%]
Primary aim of study	To test hypothesis that SCS is more likely to result in successful pain relief than reoperation
Primary study outcome	At least 50% pain relief plus patient satisfaction
Other study outcomes	Crossover to alternative treatment group of trial, pain related to daily activities, patient self-reported neurological function, medication use, employment status, complications
Intervention (description)	SCS plus CMM (analgesics and physical therapy as for control group). If test stimulation failed, patients could immediately cross over to control treatment
SCS details	Test stimulation: percutaneous placement of a temporary electrode (3847A Pisces-Quad, Medtronic) for at least 3 days – patients reporting at least 50% pain relief and demonstrating stable or improved analgesic medication intake with improved physical activity commensurate with neurological status and age, received permanent implant Permanent implant 3487A-56 or 3587A. Resume electrode, Xtrel or Itrel pulse generator (Medtronic)
Comparator	Reoperation: laminectomy and/or foraminotomy and/or discectomy in all patients with/without fusion, with/without instrumentation Patients could cross over to SCS after a 6-month postoperative period Plus CMM: standard postoperative analgesics, preoperative analgesics (tapered as rapidly as possible); physical therapy in accordance with the postspinal surgery physical therapy protocol of the institution

Table 56 *Failed back surgery syndrome: trial participants – PROCESS[59]*

Trial name	PROCESS[59]
Number randomised (total)	100
Number randomised: intervention group	52
Number randomised: control group	48
Number receiving treatment according to allocation: intervention group	Test stimulation *n* = 52 – nine failed, but five of these requested and received permanent implant Permanent implant *n* = 48 By 6-month follow-up, two of these withdrew consent (treatment ended) (*n* = 46), by 12-month follow-up *n* = 45
Number receiving treatment according to allocation: control group	Started treatment *n* = 48 By 6-month follow-up, four withdrew consent (*n* = 44), by 12-month follow-up (28 had crossed to SCS) *n* = 16
Inclusion/exclusion criteria	Inclusion criteria: neuropathic pain of radicular origin (radiating in dermatomal segments L4 and/or L5 and/or S1) predominantly in the legs (exceeding back pain), intensity of at least 50 mm on VAS 0–100 mm, documented history of nerve injury, i.e. root compression by herniated disc, competent to explain the complaint of radiating pain, neuropathic nature of pain checked as per routine practice at the centre (i.e. by clinical investigation of pain distribution, examination of sensory/motor/reflex change, with supporting tests, e.g. X-ray, magnetic resonance imaging and electromyography); pain duration at least 6 months (after a minimum of one anatomically successful surgery for a herniated disc); prior therapy at least one anatomically successful surgery for a herniated disc; aged 18 or over. Exclusion criteria: another clinically significant or disabling chronic pain condition; expected inability to receive or operate the SCS system; history of a coagulation disorder, lupus erythematosus, diabetic neuropathy, rheumatoid arthritis, or ankylosing spondylitis; active psychiatric disorder, another condition known to affect the perception of pain, or inability to evaluate treatment outcome; life expectancy of less than 1 year; existing or planned pregnancy.
Characteristics of participants at baseline – intervention group: age	Mean 48.9 years (SD 10)
Characteristics of participants at baseline – control group: age	Mean 52.0 years (SD 10.7)
Characteristics of participants at baseline – intervention group: sex	Female 22 (42%); male 30 (58%)
Characteristics of participants at baseline – control group: sex	Female 27 (56%); male 21 (44%)
Characteristics of participants at baseline – intervention group: condition/other	Time since last surgery – years mean (SD) 4.7 (5.1) > 1 surgery – *n* (%) 28 (54) Currently employed – *n* (%) 12 (23) History of legal action related to back pain – *n* (%) 5 (10) Unilateral leg pain – *n* (%) 33 (63) Bilateral leg pain – *n* (%) 19 (37) Back pain VAS – mean (SD) 54.5 (24.3) Leg pain VAS – mean (SD) 76.0 (13.0)

continued

Table 56 *Failed back surgery syndrome: trial participants – PROCESS[59] (continued)*

Trial name	PROCESS[59]
Characteristics of participants at baseline – control group: condition/other	Time since last surgery – years mean (SD) 4.6 (4.3) > 1 surgery – *n* (%) 22 (46) Currently employed – *n* (%) 10 (21) History of legal action related to back pain – *n* (%) 8 (17) Unilateral leg pain – *n* (%) 32 (67) Bilateral leg pain – *n* (%) 16 (33) Back pain VAS – mean (SD) 44.8 (23.2) Leg pain VAS – mean (SD) 73.4 (14.0)

Table 57 *Failed back surgery syndrome: trial participants – North[62]*

Trial name	North[62]
Number randomised (total)	60
Number randomised: intervention group	30
Number randomised: control group	30
Number receiving treatment according to allocation: intervention group	Test stimulation *n* = 24 (six could not get authorisation from insurance company/stroke), seven failed test stimulation, of these five crossed over to reoperation, two lost to follow-up Permanent implant *n* = 17
Number receiving treatment according to allocation: control group	Started treatment *n* = 26 (four could not get authorisation from insurance company/stroke) (14 who had had reoperation later crossed over to SCS)
Inclusion/exclusion criteria	Inclusion criteria: surgically remediable nerve root compression, concordant complaints of persistent or recurrent radicular pain, with or without low back pain, meeting criteria for surgery – pain refractory to conservative care, with neurological, tension and/or mechanical signs and imaging findings of neural compression; previous therapy one or more lumbosacral spine surgeries. Exclusion criteria: disabling neurological deficit in distribution of nerve root(s) caused by surgically remediable compression; radiographically demonstrated critical cauda equina compression; radiographic evidence of gross instability necessitating fusion; dependency on narcotic analgesics or benzodiazepines; major untreated psychiatric disorder; concurrent clinically significant or disabling chronic pain; chief complaint of axial (low back) pain exceeding radicular pain
Characteristics of participants at baseline – group not indicated	Of the 60 randomised patients (not all received treatment) age range 26–76 years, 30 female, 30 male

Table 58 *Failed back surgery syndyrome: trial results – PROCESS*[59]

Trial name	PROCESS[59]
Pain outcome – VAS (details)	Patient self-completed questionnaires, VAS 0–100 mm, three times per day separately for back and leg pain during 4 days preceding a study visit
Pain results VAS: intervention group	At 6 months, achieving 50% or more leg pain relief $n = 24$ (48%)
	At 6 months ITT 'worst-case' analysis 24/52 (46%)
	At 6 months per treatment analysis mean back pain 40.6 (SD 24.9), mean leg pain 39.9 (SD 26.3)
	At 12 months, achieving 50% or more leg pain relief, per treatment analysis 48% of 71 patients, post hoc modified ITT analysis (where patients who crossed over at 6 months were categorised as primary outcome failures according to their initial random allocation) 34%
Pain results VAS: control group	At 6 months, achieving 50% or more leg pain relief $n = 4$ (9%) (excluding five patients who failed SCS test stimulation 51%)
	At 6 months ITT 'worst-case' analysis 8/48 (17%)
	At 6 months per treatment analysis mean back pain 51.6 (SD 26.7), mean leg pain 66.6 (SD 24.0)
	At 12 months, achieving 50% or more leg pain relief, per treatment analysis 18% of 17 patients, post hoc modified ITT analysis 7%
Pain results VAS: comparison between groups	At 6 months, achieving 50% or more leg pain relief between group risk difference 39% (99% CI 18–60%); OR 9.23 (99% CI 1.99–42.84); $p < 0.001$ (excluding five patients who failed SCS test stimulation $p < 0.001$)
	At 6 months ITT 'worst-case' analysis $p = 0.002$.
	[Subgroup analysis patients with either fewer than three back surgeries or a diagnosis of FBSS of less than 12 months duration, trend that these patients were more likely to achieve success with SCS than others; however, the interaction for these subgroups was non-significant (number of back surgeries, $p = 0.95$; duration of FBSS, $p = 0.20$)]
	At 6 months per treatment analysis, compared with control group, SCS group patients experienced lower mean levels of back pain [difference in means –11.0 (99% CI –25.0 to 3.0) $p = 0.008$] and leg pain [difference in means –26.7 (99% CI –40.4 to –13.0) $p < 0.0001$]
	At 12 months, achieving 50% or more leg pain relief, per treatment analysis $p = 0.03$, post hoc modified ITT analysis $p = 0.005$
Pain outcome – pain relief/ patient satisfaction (details)	Patient satisfaction with treatment ('are you satisfied with the pain relief provided by your treatment?' and 'based on your experience so far, would you have agreed to this treatment?')
Pain results pain relief/patient satisfaction: intervention group	Satisfied with pain relief $n = 33$ (66%)
	Agree with treatment $n = 43$ (86%)
Pain results pain relief/patient satisfaction: control group	Satisfied with pain relief $n = 8$ (18%)
	Agree with treatment $n = 22$ (50%)
Pain results pain relief/patient satisfaction: comparison between groups	At 6 months, satisfied with pain relief between group risk difference (99% CI) 48% (25–71%), OR 8.73 (99% CI 2.46–31.01) $p < 0.001$
	Agree with treatment between group risk difference (99% CI) 36% (13–59%), OR 6.14 (99% CI 1.66–22.67) $p < 0.001$
Medication use outcome – details	Use of pain medication, number of patients taking any medication and daily dose of opioids were also recorded. All opioid doses were converted to a morphine equivalent dose; a range was provided for some drugs so low and high morphine equivalent scores were calculated.

continued

Table 58 *Failed back surgery syndyrome: trial results – PROCESS[59] (continued)*

Trial name	PROCESS[59]
Medication use results: intervention group	Morphine (oral equivalent daily mg) change from baseline – mean (SD)
	Low 68.3 (139) $p = 0.89$
	High 76.8 (146) $p = 0.92$
	Drug therapy – change from baseline *n* (%) Opioids 28 (56%) $p = 0.11$
	Non-steroidal anti-inflammatory drugs 17 (34%) $p = 0.58$
	Antidepressants 17 (34%) $p = 0.63$
	Anticonvulsants 13 (26%) $p = 0.18$
Medication use results: control group	Morphine (oral equivalent daily mg) change from baseline – mean (SD)
	Low 96.9 (214) $p = 0.19$
	High 125 (281) $p = 0.23$
	Drug therapy – change from baseline n (%)
	Opioids 31 (70%) $p = 0.13$; NSAIDs 22 (50%) $p = 1.00$
	Antidepressants 24 (55%) $p = 0.69$
	Anticonvulsants 22 (50%) $p = 0.06$
Medication use results: comparison between groups	At 6 months (adjusted for baseline and covariates)
	Morphine (oral equivalent daily mg) – between group difference in means
	Low –28.6 (–125.5 to 68.3) $p = 0.21$
	High –48.4 (–167.8 to 71.1) $p = 0.20$
	Drug therapy – between group risk difference (99%CI), OR (99%CI)
	Opioids –15% (–40 to 11%), OR 0.53 (0.17 to 1.64) $p = 0.20$
	Non-steroidal anti-inflammatory drugs –16% (–42 to 10%), OR 0.52 (0.17 to 1.54) $p = 0.14$
	Antidepressants –21% (–47 to 5%), OR 0.43 (0.14 to 1.28) $p = 0.06$
	Anticonvulsants –35% (–49 to 1%), OR 0.35 (0.11 to 1.10) $p = 0.02$
Physical and functional abilities outcome ODI (details)	Oswestry Disability Index version 2 (ODI) to assess functional capacity (Fairbank and Pynsent, 2000[94])
Physical and functional abilities results ODI: intervention group	Mean 44.9 (SD 18.8) change from baseline $p < 0.001$
Physical and functional abilities results ODI: control group	Mean 56.1 (SD 17.9) change from baseline $p = 0.85$
Physical and functional abilities results ODI: comparison	At 6 months, between group risk difference – 11.2 (99% CI –21.2 to – 1.3) SCS group showed a significantly greater improvement in function compared with CMM patients ($p = 0.0002$)
Physical and functional abilities outcome work status (details)	Patient self-reported employment status

Table 58 *Failed back surgery syndyrome: trial results – PROCESS[59] (continued)*

Trial name	PROCESS[59]
Physical and functional abilities results work status: intervention group	Return to work $n = 4$ out of 36 not working at baseline (11%)
Physical and functional abilities results work status: control group	Return to work $n = 1$ out of 33 not working at baseline (3%)
Physical and functional abilities results work status: comparison	At 6 months, between group risk difference 8% (99% CI –7 to 22%), OR 4.00 (99% CI 0.21 to 76.18) $p = 0.36$
Physical and functional abilities results other treatment needed (crossover for crossover trials): details	Crossover an option for either group after 6 months
Physical and functional abilities results other treatment needed (crossover for crossover trials): intervention group	$n = 5$
Physical and functional abilities results other treatment needed (crossover for crossover trials): control group	$n = 32$, four of whom failed test stimulation ($n = 28$ received SCS)
Health-related quality of life SF-36 details	Short-Form 36 (SF-36) questionnaire to assess quality of life
Health-related quality of life results SF-36: intervention group	SF-36 – mean (SD) change from baseline
	Physical function 38.1 (23.0) $p < 0.001$
	Role–physical 17.5 (32.4) $p = 0.006$
	Bodily pain 33.0 (20.9) $p < 0.001$
	General health 52.8 (22.3) $p = 0.004$
	Vitality 41.3 (21.5) $p = 0.002$
	Social functioning 49.3 (29.7) $p = 0.001$
	Role–emotional 51.3 (44.3) $p = 0.09$
	Mental health 62.6 (22.2) $p = 0.004$
Health-related quality of life results SF36: control group	SF-36 – mean (SD) change from baseline
	Physical function 21.8 (16.2) $p = 0.67$
	Role–physical 8.0 (22.7) $p = 0.67$
	Bodily pain 19.5 (12.9) $p = 0.12$
	General health 41.3 (24.4) $p = 0.007$
	Vitality 31.1 (20.9) $p = 0.97$
	Social functioning 33.5 (18.4) $p = 0.65$
	Role–emotional 29.5 (40.8) $p = 0.31$
	Mental health 50.1 (23.3) $p = 0.16$

continued

Table 58 *Failed back surgery syndyrome: trial results – PROCESS[59] (continued)*

Trial name	PROCESS[59]
Health-related quality of life results SF-36: comparison	At 6 months ITT analysis SF-36 – difference in means (99% CI)
	Physical function 16.3 (5.3 to 27.2) $p < 0.001$
	Role–physical 9.5 (–5.9 to 24.9) $p = 0.12$
	Bodily pain 13.4 (3.9 to 23.0) $p < 0.001$
	General health 11.5 (–1.2 to 24.1) $p < 0.001$
	Vitality 10.2 (–1.4 to 21.7) $p = 0.01$
	Social functioning 15.7 (2.1 to 29.4) $p = 0.002$
	Role–emotional 21.8 (–1.4 to 45.0) $p = 0.02$
	Mental health 12.5 (0.1 to 24.8) $p = 0.002$.
	Results at 3 months were similar to those at 6 months.
Complications and adverse effects outcomes SCS group	Eighty-four patients received an electrode (during test stimulation, SCS group, or crossover from CMM) during the 12 months of the study
	$n = 27$ (32%) experienced a total of 40 device-related complications
	$n = 20$ (24%) required surgery to resolve
	Principal complications: electrode migration (10%); infection or wound breakdown (8%); loss of paraesthesia (7%)
	Device-related events (number of events): Total hardware-related 13, Lead migration 10, Lead/extension fracture/torqued contacts 2, Implanted pulse generator (IPG) migration 1
	Loss of therapeutic effect, loss of paraesthesia, or unpleasant paraesthesia 6, Techniques 5, Total biological 16, Infection/wound breakdown 7, Pain at IPG/incision site 5, Neurostimulator pocket – fluid collection 4
	Number of patients (from $n = 52$) experiencing one or more non-device-related events 18 (35%)
	Patients with one or more drug adverse events 2 (4%); Drug adverse events 2
	Patients with one or more event of extra pain 0 (0%); Events of extra pain 0
	Patients with one or more new illness/injury/condition 13 (25%)
	Events of new illness/injury/condition 16
	Patients with one or more worsening of pre-existing condition 7 (13%)
	Events of worsening of pre-existing condition 7
Adverse effects: control group	Number of patients (from $n = 48$) experiencing one or more non-device related event 25 (52%)
	Patients with one or more drug adverse events 10 (21%)
	Drug adverse events 12
	Patients with one or more events of extra pain 2 (4%)
	Events of extra pain 2

Table 58 *Failed back surgery syndyrome: trial results – PROCESS[59]*

Trial name	PROCESS[59]
	Patients with one or more new illness/injury/condition 11 (23%)
	Events of new illness/injury/condition 13
	Patients with one or more worsening of pre-existing condition 7 (15%)
	Events of worsening of pre-existing condition 10
Deaths during follow-up period	0 (at 12 months)

Table 59 *Failed back surgery syndyrome: trial results – North[62]*

Trial name	North[62]
Pain outcome – pain relief/ patient satisfaction (details)	At least 50% pain relief plus patient satisfaction defined by 'considering the overall pain relief you have received from this procedure and considering the operation(s), hospitalisation(s), discomfort and expense involved would you go through it all again for the result you have obtained?'
Pain results pain relief/patient satisfaction: intervention group	Excluding patients lost to follow-up Achieving 'success' $n = 9$ of 19 (47%)
	Assuming patients lost to follow-up failed Achieving 'success' $n = 9$ of 23 (39%)
Pain results pain relief/patient satisfaction: control group	Achieving 'success' $n = 3$ of 26 (12%)
Pain results pain relief/patient satisfaction: comparison between groups	Follow-up mean 2.9 years, SCS significantly more patients achieving success than reoperation (excluding patients lost-to follow-up $p = 0.01$, Analysis assuming patients lost to follow-up failed $p = 0.04$)
Pain outcome – pain related to activities of daily living	Patient self-reported change in pain while performing everyday activities (work, walk, climb stairs, sleep, sex, drive a car, sit at table), reported as better/unchanged/worse
Pain results: comparison between groups	Non-significant difference between groups
Medication use outcome – details	Opioid analgesic use
Medication use results: intervention group	Opioid use stable or decreased $n = 20$ (out of 23) (87%); opioid use increased $n = 3$ (out of 23) (13%)
Medication use results: control group	Opioid use stable or decreased $n = 15$ (out of 26) (58%); opioid use increased $n = 11$ (out of 26) (42%)
Medication use results: comparison between groups	At mean 2.9 years Control required an increase in opiate analgesics significantly more often than SCS group ($p = 0.025$)
Physical and functional abilities outcome neurological status (details)	Patient self-report neurological function (lower extremity strength and co-ordination, sensation, bladder/bowel function)
Physical and functional abilities results neurological status: comparison	Non-significant difference between groups
Physical and functional abilities outcome work status (details)	Patient self-reported employment status
Physical and functional abilities results work status: comparison	Non-significant difference between groups. At baseline 52% retired/permanently disabled. Study end – 1 dropped out from employment, one increased from part-time to full-time employment

continued

Table 59 *Failed back surgery syndyrome: trial results – North[62] (continued)*

Trial name	North[62]
Physical and functional abilities results other treatment needed (crossover for crossover trials): details	Crossover an option from SCS immediately after test stimulation failing, or from control (reoperation) after 6 months
Physical and functional abilities results other treatment needed (crossover for crossover trials): intervention group	$n = 5$ (out of 24) (crossover rate 21%)
Physical and functional abilities results other treatment needed (crossover for crossover trials): control group	After 6 months $n = 14$ (out of 26) (crossover rate 54%) 1 additional wanted to cross over but did not get authorisation during trial period.
Physical and functional abilities results other treatment needed (crossover for crossover trials): comparison	Patients randomised to control (reoperation) were more likely to cross over than those randomised to SCS ($p = 0.02$)
Complications and adverse effects outcomes SCS group	One patient developed infection at receiver site (surgical replacement with no further complication); 3 patients (9% permanent implants) underwent hardwire revisions because of technical problems (electrode migration or malposition)
Deaths during follow-up period	One patient died of cardiac event just before 6-month follow-up test – SCS group (allocated and received SCS treatment)

Appendix 5.2: Data extraction: complex regional pain syndrome type I

Table 60 *Complex regional pain syndrome type I: trial details*

Trial name	**Kemler[65]**
Publication type of main reference (i.e. full report or abstract)	Kemler *et al*., 2000;[65] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, the Netherlands
Power calculation (priori sample calculation)	Sample size required 51 (assuming 33% assigned to SCS would fail test stimulation, 34 SCS and 17 control, for power of 90% to detect 2.3-cm difference between groups at two-tailed alpha 0.05)
Primary aim of study	To determine whether SCS plus physical therapy is more effective than physical therapy alone in treating CRPS
Primary study outcome	VAS pain intensity change from baseline
Other study outcomes	McGill pain questionnaire, global perceived effect, Jebsen functional status for hand, specially devised measure of functional status for foot, Nottingham Health profile, EuroQol 5D, short version of Sickness Impact Profile, Self-rating Depression Scale, complications
Intervention (description)	SCS and physical therapy (physical therapy as for control group). SCS device only implanted if a test stimulation was successful
SCS details (device and implantation)	Test stimulation: temporary electrode (model 3861, Medtronic), external stimulator (model 3625, Medtronic), test period at least 7 days, temporary lead removed. Permanent implant is at least 50% pain relief during last 4 days of test period, or much improved global perceived effect. (If failed test stimulation, then treated with physical therapy alone) Permanent implant: electrode (model 3487A, Medtronic), pulse generator (Itrel III, model 7425, Medtronic), implanted subcutaneously, connected to the electrode by a tunnelled extension lead (model 7495–51/66, Medtronic), console programmer (model 7432, Medtronic)
Control (description)	Physical therapy. Standardised program of graded exercises to improve strength, mobility, and function of affected hand or foot, 30 minutes twice a week, with a minimum of 2 days between sessions. Intensity reduced if pain during exercise had not returned to the pre-exercise level within 24 hours. Physical therapy total duration 6 months, starting after the second assessment, continuation after 6 months was optional. To ensure standardisation, physical therapists were trained

Table 61 *Complex regional pain syndrome type I: trial participants*

Trial name	**Kemler[65]**
Number randomised (total)	54
Number randomised: intervention group	36
Number randomised: control group	18
Number receiving treatment according to allocation: intervention	Test stimulation *n* = 36 Permanent implant *n* = 24 (other 12 control treatment)
Number receiving treatment according to allocation: control	18
Inclusion/exclusion criteria	Inclusion criteria: chronic regional pain syndrome type 1 meeting diagnostic criteria of International Association for the Study of Pain; mean pain intensity at least 5 cm on VAS from 0 to 10 cm, cold/warm/intermittently cold and warm feeling in affected area; disease that was clinically restricted to one hand or foot and affected the entire hand or foot, additionally with impaired function and symptoms beyond the area of trauma. Also three of the following: oedema; increased nail growth; increased hair growth; hyperhidrosis; abnormal skin colour; hypoaesthesia; hyperalgesia; mechanical and/or thermal allodynia; patchy demineralisation of bone. Pain duration at least 6 months; did not have a sustained response to standard therapy (6 months of physical therapy, sympathetic blockade, transcutaneous electrical nerve stimulation, and pain medication); aged 18–65 years Exclusion criteria: Raynaud's disease; current or previous neurological abnormalities unrelated to reflex sympathetic dystrophy;, another condition affecting the function of the diseased or contralateral extremity; a blood-clotting disorder or use of an anticoagulant drug; use of a cardiac pacemaker.
Characteristics of participants at baseline – intervention group: age	Mean 40 years (SD 12)
Characteristics of participants at baseline – control group: age	Mean 35 years (SD 8)
Characteristics of participants at baseline – intervention group: sex	Male 14 (39%); female 22 (61%)
Characteristics of participants at baseline – control group: sex	Male 3 (17%); female 15 (83%)
Characteristics of participants at baseline – intervention group: other	Duration of disorder mean 40 months (SD 28) Location hand 22 (61%), foot 14 (39%) Score on the 90-item Symptom Check List (SCL-90, a scale of 90–450 with higher score indicating greater psychological distress) mean 143 (SD 28) Pain score on VAS 0–10 cm mean 7.1 cm (SD 1.5) Health-related quality of life VAS 0–100 mm mean 47 (SD 19)
Characteristics of participants at baseline – control group: other	Duration of disorder mean 34 months (SD 22) Location hand 11 (61%), foot 7 (39%) Score on the SCL-90 mean 146 (SD 32) Pain score on VAS 0–10 cm mean 6.7 cm (SD 1.2) Health-related quality of life VAS 0–100 mm mean 42 (SD 19)
Characteristics of participants at baseline – group not indicated	CRPS precipitated by trauma *n* = 26, by surgery *n* = 24, developed spontaneously *n* = 4 All patients had severe pain and functional impairment that made them unable to work. Of 33 patients with affected hand, 20 unable to use for any daily activity; 13 used a splint. Of 21 patients with affected foot, 10 used a wheelchair, 8 used crutches.

Table 62 *Complex regional pain syndrome type I: trial results*

Trial name	**Kemler[65]**
Pain outcome – VAS (details)	Intensity of pain assessed on a VAS from 0 cm (no pain) to 10 cm (very severe pain)
Pain results VAS: intervention group	At 6 months ($n = 36$, 24 of whom had SCS implant) mean reduction of 2.4 cm in the intensity of pain At 2 years ($n = 35$, 24 of whom had SCS implant) mean intensity reduced by 2.1 cm (mean 2.1, SD 2.8)[67] At 5 years ($n = 31$, 22 of whom had SCS implant) mean pain intensity reduced from baseline by 1.7 cm (at 3 years – 1.6 cm, at 4 years – 1.7 cm)[66] Per treatment analysis at 6 months decreased by a mean of 3.6 cm ($p < 0.001$). Per treatment analysis at 2 years mean pain reduction 3 cm (SD 2.7)[67]
Pain results VAS: control group	At 6 months ($n = 18$) mean increase of 0.2 cm in the intensity of pain At 2 years ($n = 16$) no change in mean pain intensity mean 0 cm (SD 1.5)[67] At 5 years ($n = 13$) mean pain intensity reduced from baseline by 1.0 cm (at 3 years –0.7 cm, at 4 years – 1.0 cm)[66]
Pain results VAS: comparison between groups	At 6 months $p < 0.001$ At 2 years $p = 0.001$[67] At 5 years $p = 0.25$ (at 3 years $p = 0.29$, at 4 years $p = 0.42$)[66] Per treatment analysis at 6 months $p < 0.001$ Per treeatment analysis at 2 years $p < 0.001$[67]
Pain outcome – McGill (details)	McGill Pain Questionnaire including pain-rating index At 6 months non-significant difference between groups Per treatment analyses at 6 months and at 2 years, SCS significant improvement in pain-rating index ($p = 0.02$)[67]
Global perceived effect	Patients rated the global perceived effect on a seven-point scale (1, worst ever; 2, much worse; 3, worse; 4, not improved and not worse; 5, improved; 6, much improved; and 7, best ever)
Global perceived effect results: intervention group	At 6 months proportion of patients with a score of 6 ('much improved') 14 patients (39%) At 2 years $n = 15$ of 35 (43%)[67] Per treatment analysis at 6 months $n = 14$ (58%)
Global perceived effect results: control group	At 6 months proportion of patients with a score of 6 ('much improved') 1 patient (6%) At 2 years 1 of 16 (6%)[67]
Global perceived effect results: comparison between groups	At 6 months proportion of patients with a score of 6 ('much improved') $p = 0.01$ At 2 years $p = 0.001$[67] Per treatment analysis at 6 months $p < 0.001$ Per treatment analysis at 2 years $p < 0.001$[67]

continued

Table 62 *Complex regional pain syndrome type I: trial results (continued)*

Trial name	Kemler[65]
Physical and functional abilities outcome – Jebsen for hand, specially devised for foot	Jebsen functional test for the hand, specially devised test for the foot. For both procedures, mean of subtest times is final result. Used goniometry to measure range of motion of both ankles or both wrists and all finger joints. Used a Jamar dynamometer to measure grip strength, and a hand-held myometer to measure strength of foot dorsiflexion and plantar flexion
Physical and functional abilities results: intervention group	At 6 months: Hand – function seconds required to perform task mean 2 (SD 10); strength mean 3 kg (SD 8); range of motion wrist mean 2 degrees (SD 10); range of motion all fingers mean 23 degrees (SD 181). Foot – function seconds required to perform task mean 1 second (SD 3); dorsiflexion N 14 (28); plantar flexion N 23 (63); range of motion ankle mean 11 degrees (SD 18) At 2 years: Upper extremities – functional score (from $n = 21$), upper extremities: function mean 2 seconds (SD 14); strength 0 kg (SD 5); range of motion wrist 0 degrees (30); range of motion hand – 18 degrees (181). Lower extremities – functional score (from $n = 14$): function – 3 seconds (SD 4); dorsiflexors N 11 (27); plantar flexors N 14 (43); range of motion ankle 0 degrees (SD 16)[67] Per treatment analysis at 6 months treatment did not result in any functional improvement
Physical and functional abilities results: control group	At 6 months: Hand – function seconds required to perform task mean – 1 (SD 5); strength mean 1 kg (SD 3); range of motion wrist mean – 3 degrees (SD 30); range of motion all fingers mean – 39 degrees (SD 190). Foot – function seconds required to perform task mean – 1 second (SD 3); dorsiflexion N 3 (4); plantar flexion N 40 (51); range of motion ankle mean 8 degrees (SD 10) At 2 years: Upper extremities – functional score (from $n = 10$), function mean 4 seconds (SD 21); strength – 1 kg (SD 3); range of motion wrist – 5 degrees (37); range of motion hand – 119 degrees (309). Lower extremities – functional score (from $n = 5$): function – 5 seconds (SD 5); dorsiflexors N 8 (27); plantar flexors N 20(44); range of motion ankle 13 degrees (SD 8)[67]
Physical and functional abilities results: comparison	At 6 months: no clinically important improvement in functional status, Hand – function seconds required to perform task $p = 0.21$; strength kg $p = 0.44$; range of motion wrist degrees $p = 0.61$; range of motion all fingers degrees $p = 0.38$. Foot – function seconds required to perform task $p = 0.96$; dorsiflexion $p = 0.16$; plantar flexion $p = 0.54$; range of motion ankle degrees $p = 0.71$ At 2 years: Upper extremities – functional score (from $n = 10$), function $p = 0.78$; strength $p = 0.54$; range of motion wrist $p = 0.73$; range of motion hand $p = 0.36$. Lower extremities – functional score (from $n = 5$), function $p = 0.48$; dorsiflexors $p = 0.21$; plantar flexors $p = 0.80$; range of motion ankle $p = 0.04$[67]
Health-related quality of life outcome (includes depression outcome) (details)	Nottingham Health Profile, EuroQol 5D, short version of the Sickness Impact Profile, Self-Rating Depression Scale
Health-related quality of life score results: intervention group	At 6 months ($n = 36$) change in HRQoL% mean 6 (SD 22) At 2 years ($n = 35$) change in HRQoL% mean 7 (SD 20)[67]
Health-related quality of life score results: control group	At 6 months ($n = 18$) change in HRQoL% mean 3 (SD 18) At 2 years ($n = 16$) change in HRQoL% mean 12 (SD 18)[67]
Health-related quality of life results: comparison	At 6 months change in HRQoL% $p = 0.58$ At 2 years $p = 0.41$[67] Per treatment analysis at 6 months, and at 2 years, SCS more improvement than control group (the pain component of the Nottingham Health Profile) for both patients with an affected hand ($p = 0.02$) and those with an affected foot ($p = 0.008$)

Table 62 *Complex regional pain syndrome type I: trial results (continued)*

Trial name	**Kemler[65]**
Complications and adverse effects outcomes SCS group	Test stimulation 4 patients dural puncture Of *n* = 24 with permanent implant. At 6 months, implantation was complicated by dural puncture in two patients (with headache in one). Six (25%) had a total of 11 other complications. Four patients had long-term complications, 1 of these clinical signs of infection, required antibiotics and removal of implant (later had reimplantation), 2 other patients painful pulse-generator pocket was modified, and 1 patient, a defective lead was replaced. Complications related to unsatisfactory positioning of the electrode, 5 patients (surgical correction successful in 4 of the 5 patients; correct positioning required three procedures in the 5th patient) During 2-year follow-up SCS complications requiring reoperation 9 patients: 8 repositioning of lead; 7 revision of pulse generator pocket; 2 replacement lead; 3 explanation system; 1 reimplantation system; 1 replacement pulse generator. Side effects: 19 change of amplitude by bodily movements; 13 paraesthesia in other body parts; 11 pain/irritation from extension lead or plug; 10 pain/irritation from pulse generator; 7 more pain in other body parts; 4 disturbed urination; 3 movements or cramps resulting from elevated amplitude[67]
Deaths during follow-up period	None reported

Appendix 5.3: Data extraction: critical limb ischaemia

Table 63 *Critical limb ischaemia: trial details – ESES[68]*

Trial name	ESES[68]
Publication type of main reference (i.e. full report or abstract)	Spincemaille *et al*., 2000;[68] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Multicentre, 17 centres, the Netherlands
Power calculation (priori sample calculation)	Sample size required 112 (56 per treatment arm, to detect group difference in limb survival, assuming hazard ratio of 2, two-sided alpha of 5% and power 80%)
Primary aim of study	To test the effect of adding SCS to CMM compared with CMM alone
Primary study outcome	Limb salvage rates, pain relief – VAS, McGill
Other study outcomes	Nottingham Health Profile, EuroQol, mobility subscore of the Sickness Impact Profile, complications, adverse effects
Intervention (description)	SCS plus CMM (as for control group)
SCS details (device and implantation)	Permanent implant: lead (Quadripolar, Medtronic), pulse generator (Itrel II, Medtronic) was implanted subcutaneously
Control (description)	CMM. Included care for wound ulcers, pain medication (minor and major analgesics), antithrombotic drugs, vasoactive drugs, antibiotics as needed. List of recommended medication provided but no fixed treatment regimen. Chemical lumbar sympathectomy and prostanoids not excluded but used in only three patients

Table 64 *Critical limb ischaemia: trial details – Suy[73]*

Trial name	Suy[73]
Publication type of main reference (i.e. full report or abstract)	Suy *et al*., 1994;[73] book chapter
Study design	Prospective RCT
Setting	Multicentre, 3 centres, Belgium
Power calculation (priori sample calculation)	NR
Primary aim of study	To evaluate the possible benefit of SCS on severe limb ischaemia
Primary study outcome	Limb salvage rates
Other study outcomes	Complications
Intervention (description)	SCS plus CMM (as for control group)
SCS details (device and implantation)	Permanent implant: Medtronic model 3578A (Resume) leads; 11 patients bipolar implanted pulse generator (IPG) model 7420, 9 patients programmable IPG model 7424
Control (description)	CMM. Appropriate antiaggregation therapy, rheological medication, analgesic therapy, including toe amputation if necessary

Table 65 *Critical limb ischaemia: trial details – Jivegard*[74]

Trial name	**Jivegard**[74]
Publication type of main reference (i.e. full report or abstract)	Jivegard *et al*., 1995;[74] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Two centres, Sweden
Power calculation (priori sample calculation)	Sample size required approximately 50 (alpha < 5% and power > 80%)
Primary aim of study	To test hypothesis that SCS improves limb salvage in patients with inoperable severe limb ischaemia
Primary study outcome	Limb salvage rates
Other study outcomes	Pain VAS 0–100 mm and rating on 5-point scale, skin temperature VAS 0–100, ankle to brachial pressure index, systolic toe to brachial pressure index, complications
Intervention (description)	SCS and peroral analgesic treatment (as for control group)
SCS details (device and implantation)	Permanent implant: pulse generator (Medtronic Quad + Itrel II, Medtronic) implanted subcutaneous
Control (description)	Peroral analgesic treatment, prescribed as required by the patient: usually dextropropoxyphen as first choice and opiates as second. Ischaemic ulcers treated by specially assigned nurse

Table 66 *Critical limb ischaemia: trial details – Claeys*[76]

Trial name	**Claeys**[76]
Publication type of main reference (i.e. full report or abstract)	Claeys and Horsch, 1999;[76] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, Germany
Power calculation (priori sample calculation)	NR
Primary aim of study	To evaluate the efficacy of SCS on ulcer healing and limb salvage
Primary study outcome	Limb salvage rates
Other study outcomes	Ankle to brachial pressure index, complications, adverse effects
Intervention (description)	SCS (plus prostaglandin E1 and standard wound care)
SCS details (device and implantation)	Test stimulation: quadripolar lead (Pisces Quad 387A, Medtronic) percutaneous, trial period of 1 week when patient experienced adequate pain relief then permanent implant. Permanent implant: implantable pulse generator (Itrel II, Medtronic) subcutaneously
Control (description)	Prostaglandin E1 and standard wound care

Table 67 *Critical limb ischaemia: trial participants – ESES*[68]

Trial name	ESES[68]
Number randomised (total)	120
Number randomised: intervention group	60
Number randomised: control group	60
Number receiving treatment according to allocation: intervention	Permanent implant $n = 59$ (1 refused) of these $n = 8$ had problems leading to suboptimal stimulation(4 – no proper lead positioning resulting in paraesthesias covering the pain region, 4 – positioning not optimal and renewed intervention did not correct the problem; so patients with implant and optimal stimulation $n = 51$)[69]
Number receiving treatment according to allocation: control	60
Inclusion/exclusion criteria	Inclusion criteria: surgically non-reconstructible atherosclerotic vessel disease in one of the lower limbs – diagnosed as having critical ischaemia as defined by the European consensus; persistent rest pain for at least 2 weeks, being treated with analgesics and/or ulceration or gangrene of foot or toes which surface may not exceed 3 cm^2; dropper ankle systolic pressure less than or equal to 50 mmHg or ankle to brachial pressure index less than 35%, for patients with diabetes and incompressible vessels, leading to unreliable ankle pressure; absence of arterial ankle pulsations Exclusion criteria: vascular disorders other than atherosclerotic disease; Intractable existing infections of the ulcerations or gangrene area; neoplastic or concomitant disease restricting life expectancy to less than a year; p resence of a cardiac pacemaker; Inadequate patient compliance as the result of psychological or social incompetence
Characteristics of participants at baseline – intervention group: age	Mean age 73 years (SD 9.8)
Characteristics of participants at baseline – control group: age	Mean age 72 years (SD 10.6)
Characteristics of participants at baseline – intervention group: sex	Female 27 (45%); male 33 (55%)
Characteristics of participants at baseline – control group: sex	Female 23 (38%); male 37 (62%)
Characteristics of participants at baseline – intervention group: other	Diabetes 37% ($n = 22$) Contralateral leg: symptomatic 32% (Spincemaille *et al*., 19), amputated 15% ($n = 9$) Smoking status: not for > 1 year 37% ($n = 22$), still smoking 30% ($n = 18$) Cerebrovascular accident/transient ischaemic attack 22% ($n = 13$) Myocardial infarction 38% ($n = 23$); angina pectoris 20% ($n = 12$); ulcerations/gangrene 63% ($n = 38$); dry gangrene 40% ($n = 24$), wet gangrene 13% ($n = 8$) Previous vascular surgery: none 25% ($n = 15$), 1 or 2 42% ($n = 25$), > 3 32% ($n = 19$); sympathectomy (randomized leg) 35% ($n = 21$); ankle pressure (mean ± SD) 35.2 ± 24.8; ankle to brachial index (mean ± SD) 0.23 ± 0.16
Characteristics of participants at baseline – control group: other	Diabetes 38% ($n = 23$) Contralateral leg: symptomatic 48% ($n = 29$), amputated 12% ($n = 7$) Smoking status: not for > 1 year 27% ($n = 16$), still smoking 44% ($n = 26$) Cerebrovascular accident/transient ischaemic attack 27% ($n = 16$) Myocardial infarction 37% ($n = 22$); angina pectoris 25% ($n = 15$); ulcerations/gangrene 68% ($n = 41$); dry gangrene 38% ($n = 23$), wet gangrene 8% ($n = 5$) Previous vascular surgery: none 18% ($n = 11$), 1 or 2 48% ($n = 29$), > 3 33% ($n = 20$); sympathectomy (randomized leg) 32% ($n = 19$); ankle pressure (mean ± SD) 41.6 ± 21.8; ankle to brachial index (mean ± SD) 0.28 ± 0.13

Table 68 *Critical limb ischaemia: trial participants – Suy[73]*

Trial name	Suy[73]
Number randomised (total)	38
Number randomised: intervention group	20
Number randomised: control group	18
Number receiving treatment according to allocation: intervention	20
Number receiving treatment according to allocation: control	18
Inclusion/exclusion criteria	Inclusion criteria: chronic ischaemic rest pain related to peripheral vascular occlusive disease, either as the result of arteriosclerosis or arteritis (Buerger's disease); severe arteriopathy, unsuitable for vascular reconstruction, angioplasty or thrombolysis (arteriographies prior to randomisation evaluated by vascular surgeon); limitation of existing trophic lesions to superficial ulcers without involvement of tendons or bone, or to dry or wet gangrene of a toe Exclusion criteria: non reported
Characteristics of participants at baseline – intervention group: age	Mean for patients with arteriosclerosis ($n = 16$) 66 years, mean for patients with Buerger's disease ($n = 4$) 36 years, range for all patients 26–80 years
Characteristics of participants at baseline – control group: age	Mean for patients with arteriosclerosis ($n = 11$) 65 years, mean for patients with Buerger's disease ($n = 7$) 46 years, range for all patients 36–80 years
Characteristics of participants at baseline – intervention group: sex	Female 5 (25%); male 15 (75%)
Characteristics of participants at baseline – control group: sex	Female 3 (17%); male 15 (83%)
Characteristics of participants at baseline – intervention group: other	Localisation of lesions: foot arteries 3; crural arteries 5; femoropopliteal arteries 12; external iliac artery and femoropopliteal arteries 0 Symptoms: uncomplicated rest pain 5; rest pain and ulcers 6; livid cyanotic forefoot 3; dry toe gangrene 4; wet gangrene 2 Previous vascular operations: sympathectomy 8; vascular reconstruction 10; number of operations 26. Diabetes mellitus type 1 3; type 2 3. Smoking: non-smoker 3; stopped smoking 8; smoker 9
Characteristics of participants at baseline – control group: other	Localisation of lesions: foot arteries 0; crural arteries 9; femoropopliteal arteries 8; external iliac artery and femoropopliteal arteries 1 Symptoms: uncomplicated rest pain 4; rest pain and ulcers 7; livid cyanotic forefoot 2; dry toe gangrene 4; wet gangrene 1 Previous vascular operations: sympathectomy 13; vascular reconstruction 11; number of operations 23. Diabetes mellitus type 1 1; type 2 1. Smoking: non-smoker 0; stopped smoking 5; smoker 13
Characteristics of participants at baseline – group not indicated	30 of 38 patients on narcotic analgesic treatment

Table 69 *Critical limb ischaemia: trial participants – Jivegard*[74]

Trial name	Jivegard[74]
Number randomised (total)	51
Number randomised: intervention group	25
Number randomised: control group	26
Number receiving treatment according to allocation: intervention group	22
Number receiving treatment according to allocation: control group	26
Inclusion/exclusion criteria	Inclusion criteria: severe chronic lower limb ischaemia in atherosclerotic and diabetic patients with rest pain and/or ischaemic ulcerations; duration more than 2 weeks; prior therapy vascular reconstruction was considered impossible or had failed as a result of poor outflow conditions. All patients had undergone digital subtraction arteriography Exclusion criteria: rapidly progressing ischaemia, gangrene of more than one toe; extensive infection and/or extensive non-healing ischaemic ulcerations; poor co-operability; presence of associated diseases prohibiting the use of SCS
Characteristics of participants at baseline – intervention group: age	Mean age 73 years (SD 12)
Characteristics of participants at baseline – control group: age	Mean age 73 years (SD 12)
Characteristics of participants at baseline – intervention group: sex	Female 11 (44%); male 14 (56%)
Characteristics of participants at baseline – control group: sex	Female 12 (46%); male 14 (54%)
Characteristics of participants at baseline – intervention group: other	Ischaemic ulceration present $n = 13$ (52%); Diabetes $n = 5$ (20%) Arterial hypertension (data missing from 3 patients across both groups) $n = 11$ (44%); pain (VAS score 0 to 100 maximally severe pain) mean 52 (SD 5); pain score (1 to 5) mean 3.2 (SD 0.2); skin temperature (VAS score 0 to 100) mean 33 (SD 4) Ankle to brachial pressure index (ABI) in ischaemic limbs mean 0.33 (SEM 0.05); systolic toe to brachial pressure index (STPI) mean 0.08 (SEM 0.02); critical limb ischaemia according to the second European Consensus Document $n = 21$ (84%) Medication: opiates $n = 5$ (20%), dextropropoxyphen $n = 16$ (64%), paracetamol $n = 6$ (24%), acetylsalicylic acid $n = 2$ (8%)
Characteristics of participants at baseline – control group: other	Ischaemic ulceration present $n = 13$ (50%); Diabetes $n = 5$ (19%) Arterial hypertension (data missing from 3 patients across both groups) $n = 13$ (50%); Pain (VAS score 0 to 100) mean 55 (SD 5); Pain score (1 to 5) mean 3.1 (SD 0.2); Skin temperature (VAS score 0 to 100 maximally warm) mean 35 (SD 3) ABI in ischaemic limbs mean 0.37 (SEM 0.06); STPI mean 0.05 (SEM 0.01); Critical limb ischaemia according to the second European Consensus Document $n = 24$ (92%) Medication: opiates $n = 6$ (23%), dextropropoxyphen $n = 11$ (42%), paracetamol $n = 11$ (42%), acetylsalicylic acid $n = 2$ (8%)

Table 70 *Critical limb ischaemia: trial participants – Claeys*[76]

Trial name	Claeys[76]
Number randomised (total)	86 (randomisation 7 days after start of prostaglandin E1 therapy)
Number randomised: intervention group	45
Number randomised: control group	41
Number receiving treatment according to allocation: intervention group	45
Number receiving treatment according to allocation: control group	41
Inclusion/exclusion criteria	Inclusion criteria: Fontaine stage IV patients with end-stage peripheral arterial occlusive disease (PAOD) undergoing 21-day intravenous prostaglandin E1 therapy (80 μg/day) for non-healing ulcers; arteriosclerosis; non-reconstructible (unsuitable for angioplasty or crural or pedal bypass surgery) PAOD as proven by intra-arterial angiography or patient condition; ankle systolic pressure < 50 mmHg; severe rest pain despite analgesic medication, presence of non-healing foot ulcers or dry gangrene; ulcers or gangrene present for a minimum of 3 weeks Exclusion criteria: mixed type of ulceration; local infection; patients suitable for reconstructive procedures; short life expectancy; heart failure NYHA Class III–IV, renal failure; liver disease; uncontrolled hypertension; Buerger's disease; unstable angina; neuropsychiatric diseases
Characteristics of participants at baseline – intervention group: age	67.7 years (SD 11.9)
Characteristics of participants at baseline – control group: age	69.9 years (SD 10.2)
Characteristics of participants at baseline – intervention group: sex	Female 19, male 26
Characteristics of participants at baseline – control group: sex	Female 18, male 23
Characteristics of participants at baseline – intervention group: other	PAOD $n = 39$; PAOD plus diabetes mellitus $n = 6$; number of ischaemic lesions: 1 lesion $n = 37$, 2 lesions $n = 4$, 3+ lesions $n = 4$; hypertension $n = 34$; cigarette pack years 44.4; ankle pressure on the treated limb 0 mmHg $n = 12$, 20 mmHg $n = 12$, 40 mmHg $n = 21$; ankle to brachial pressure index 0.287 ± 0.19; $TcPO_2$ on the treated foot 10.0 mmHg (± 7.8); walking ability unable to walk $n = 25$, walk less than 50 m $n = 20$; mean walking distance 24 m
Characteristics of participants at baseline – control group: other	PAOD $n = 34$; PAOD plus diabetes mellitus $n = 7$; number of ischaemic lesions: 1 lesion $n = 29$, 2 lesions $n = 9$, 3+ lesions $n = 3$; hypertension $n = 36$; cigarette pack years 49.4; ankle pressure on the treated limb 0 mmHg $n = 6$, 20 mmHg $n = 10$, 40 mmHg $n = 25$; ankle to brachial pressure index 0.340 ± 0.187; $TcPO_2$ on the treated foot 11.6 mmHg (± 6.7); walking ability unable to walk $n = 32$, walk less than 50 m $n = 9$; mean walking distance 13 m

Table 71 *Critical limb ischaemia: trial results – ESES*[68]

Trial name	ESES[68]
Pain outcome – VAS (details)	VAS 0 to 10 (or 0 to 100) Pain relief of > 50% considered good, 25–50% moderate, < 25% was considered unsuccessful
Pain results VAS: intervention group	At intake 4.7 (scale 0–10, $n = 60$, SE 0.4), mean minimum pain score of 2.5 (SE 0.3) and mean maximum pain score of 8 (SE 0.2) At 1 month VAS 43.6 ($n = 47$) At 6 months, 33.5 (on scale 0–100) ($n = 44$, SE 0.4) with a minimum score of 2 (SE 0.3) and a maximum score of 5.3 (SE 0.5) At 12 months mean VAS 27.6 ($n = 42$) At 18 months VAS 22.5 ($n = 27$) After amputation the pain score declined to values between 2.6 and 1.4 for SCS treatment ($p < 0.001$)
Pain results VAS: control group	At baseline mean VAS 51.3 SE 2 (scale 0–100, $n = 58$) At 1 month 38.3 ($n = 47$) At 6 months mean VAS 25.6 (scale 0–100, $n = 42$) At 12 months mean VAS 29.8 (scale 0–100, $n = 38$) At 18 months mean VAS 25.2 SE 5 (scale 0–100, $n = 24$) After amputation the pain score declined to values between 3.9 and 1.8 in patients receiving standard treatment ($p < 0.001$)
Pain results VAS: comparison between groups	Non-significant difference between groups across 18 months
Pain outcome – McGill (details)	The pain-rating index (PRI), part I of the McGill
Pain results McGill: intervention group	PRI baseline mean 22.6 ($n = 57$, SE 1.5) At 1 month mean 17.9 ($n = 50$), at 3 months mean 11.9 ($n = 39$), at 6 months 13.2 ($n = 37$), at 12 months 11.1 ($n = 29$), at 18 months 8.7 ($n = 17$) Pain was decreased significantly at 1 month and 3 months ($p < 0.001$)[70] remaining stable up to 18 months
Pain results McGill: control group	PRI baseline mean 21.5 ($n = 58$, SE 1.5) At 1 month mean 15.8 ($n = 43$), difference 32% ($p = 0.005$), at 3 months mean 10.9 ($n = 38$), at 6 months 9.2 ($n = 36$), at 12 months 8.5 ($n = 23$), at 18 months 8.1 ($n = 17$) Pain was decreased significantly at 1 month and 3 months ($p < 0.001$)[70] remaining stable up to 18 months
Pain results McGill: comparison between groups	Non-significant between groups[70] When considering only non-amputated patients, more pain relief in the SCS than the CMM group; in the case of amputation, pain relief slightly favoured CMM (not reported as significant)
Medication use outcome – details	A Medication Quantification Scale (MQS) to evaluate the use of analgesics. Number of patients on narcotics

Table 71 *Critical limb ischaemia: trial results – ESES[68] (continued)*

Trial name	ESES[68]
Medication use results: intervention group	Baseline mean MQS 6.68 (SE 0.65), 1 month 3.5 ± 0.6, 3 months 2.8 ± 0.7, 6 months 2.0 ± 0.5, 12 months 1.7 ± 0.5, 18 months 2.4 ± 1.0 Patients in group on narcotics 18 at baseline, 10 at 1 month, 9 at 3 months, 5 at 6 months, 4 at 12 months, 2 at 18 months[70]
Medication use results: control group	Baseline mean MQS 7.35 (SE 0.68), 1 month 1 8.9 ± 0.9, 3 months 6.8 ± 0.8, 6 months 6 5.6 ± 0.9, 12 months 3.6 ± 0.8, 18 months 1.9 ± 0.7 Patients in group on narcotics 21 at baseline, 23 at 1 month, 14 at 3 months, 12 at 6 months, 6 at 12 months, 0 at 18 months[70]
Medication use results: comparison between groups	MQS significant difference between groups at 1 month and 3 months ($p < 0.001$), and 6 months ($p = 0.002$), borderline significant at 12 months ($p = 0.055$), not significant at 18 months ($p = 0.70$)
Physical and functional abilities results limb salvage rates: intervention group	Limb survival at 6 months 66%, at 1 year 60%, at 2 years 52% Events: patients with major amputation at 6 months 19 (34%), at 2 years 25 (48%)[70] Per treatment analysis, at 6 months 67%, at 2 years 55%[70] (Subgroup patients with intermediate skin microcirculation amputation rate at 18 months, per treatment 8/34 24%, ITT 7/31 23%[71])
Physical and functional abilities results limb salvage rates: control group	Limb survival at 6 months 68%, at 1 year 46%, at 2 years 46% Events: patients with major amputation at 6 months 18 (32%), at 2 years 29 (54%)[70] Per treatment analysis, at 6 months 68%, at 2 years 46% (Subgroup patients with intermediate skin microcirculation amputation rate at 18 months 14/29 48%[71])
physical and functional abilities results limb salvage rates: comparison	Non-significant difference between groups, limb survival $p = 0.47$, HR for SCS vs control group 0.81 (0.47–1.51) Per treatment analysis, at 6 months, 2 years hazard ratio 0·78 (0 44–1·39), $p = 0{\cdot}39$[70] Non-significant difference between groups on number of patients with major amputation at 6 months or 2 years $p = 0.47$[70] {Subgroup analysis in patients with intermediate skin microcirculation immediately prior to treatment, per treatment analysis at 18 months SCS treated had no significant trend for lower rate of amputation $p = 0.08$, ITT analysis $p = 0.17$ [intermediate defined as transcutaneous rest or peak oxygen pressure between 10 and 30 mmHg, or not fitting into category of poor [i.e. capillary microscopy: low capillary density (density, < 20/mm^2), or low peak erythrocyte velocity (< 50 mm/s), or no reactive hyperaemia (peak minus rest velocity, 0 or under mm/s), laser Doppler scan perfusion: no reactive hyperaemic response (peak – rest LDP, 3 or less AU)] or good [capillary microscopy: normal capillary density (density, 20 or more/mm^2), and present reactive hyperaemia (peakv – restv, > 0 mm/s) and normal peak erythrocyte velocity (50 or more mm/s), laser Doppler scan perfusion: present reactive hyperaemic response (peak – rest LDP, >3 AU)] Ubbink *et al.*, 1999[71]}
Health-related quality of life outcome Nottingham health profile (details)	The first part of the Nottingham Health Profile (NHP)

continued

Table 71 *Critical limb ischaemia: trial results – ESES[68] (continued)*

Trial name	ESES[68]
Health-related quality of life results Nottingham health profile: intervention group	Baseline overall NHP mean 48 (SE 2.6, $n = 57$). 3 to 6 months decline of mean to 35 (SE 2.6, $n = 44$) remained stable up to 18 months. Mobility score at baseline 54.5 ($n = 60$), at 1 month 52.5 ($n = 50$), at 6 months overall 50.5 ($n = 37$) [Subgroup non-amputated 51.5, amputated 64; at 12 months non-amputated 40, amputated 61.2 ($n = 29$) overall 53.7; at 18 months non-amputated 30.7, amputated 56.2 ($n = 17$)] NHP Pain Score baseline 70 ($n = 57$, SE 3.9), at 18 months 31 ($n = 27$, SE 6), significant reduction, (subgroup patients who underwent an amputation had significantly lower pain scores; $p < 0.01$)
Health-related quality of life results Nottingham health profile: control group	Baseline overall NHP mean 47 (SE 2.6, $n = 58$). 3 to 6 months decline of mean to 34 (SE 3, $n = 41$), remained stable up to 18 months. Mobility score at baseline 54 ($n = 60$), at 1 month overall 52.5 ($n = 43$) at 6 months [Subgroup non-amputated 44.5, amputated 60.5 ($n = 36$) overall 51; at 12 months non-amputated 50.5, amputated 57 overall 54 ($n = 23$); at 18 months non-amputated 49, amputated 51.5 overall 51 ($n = 17$)] NHP Pain Score baseline 72 ($n = 58$, SE 3.5), at 18 months 36 ($n = 24$, SE 6), significant reduction (Subgroup patients who underwent an amputation had significantly lower pain scores; $p < 0.01$)
Health-related quality of life results Nottingham health profile: comparison	Overall NHP non-significant between groups [Subgroup Mobility score of NHP from 6 months follow-up; patients undergoing SCS who were not amputated had better mobility and energy scores than the conservatively treated non-amputated patients ($p < 0.01$). In case of amputation, mobility was reduced and not influenced by rehabilitation programmes]
Health-related quality of life outcome EuroQol (details)	The EuroQol
Health-related quality of life results Euroqol: intervention group	Baseline value 54 ($n = 56$, SE 2.8) at 12 months 41 [Subgroup Patients who underwent an amputation early in the trial had worse initial EuroQol scores than those amputated later. Scores after amputation worsened to at $t = 1$ 61 ($n = 4$, SE 4.9) in the SCS group. Gradually, over a period of months, scores regained values comparable to those of non-amputated patients]
Health-related quality of life results EuroQol: control group	Baseline value 51 ($n = 58$, SE 2.9) at 12 months 43 [Subgroup Patients who underwent an amputation early in the trial had worse initial EuroQol scores than those amputated later. Scores after amputation worsened to 66 at $t = 1$ ($n = 8$, SE 8.2) in the standard group. Gradually, over a period of months, scores regained values comparable to those of non-amputated patients]
Health-related quality of life results EuroQol: comparison	Non-significant difference between groups
Health-related quality of life outcome Sickness Impact Profile (details)	SIP – mobility index
Health-related quality of life results Sickness Impact Profile: intervention group	Mean at intake 34 (SE 1.7, $n = 57$), non-significant decline during follow-up
Health-related quality of life results Sickness Impact Profile: control group	Mean at intake 36 (SE 1.9, $n = 58$), non-significant decline during follow-up
Health-related quality of life results Sickness Impact Profile: comparison	Non-significant difference between groups

Table 71 *Critical limb ischaemia: trial results – ESES[68] (continued)*

Trial name	ESES[68]
Complications and adverse effects outcomes SCS group	Throughout an 18-month follow-up, 25 surgery complications (6 implant failure; 13 lead displacement; 3 infection; 0 lead fracture; 3 battery EQL)[69] Eight patients (13%) had suboptimal stimulation. Side effects occurred in four patients: duodenal perforation (1), nausea (2), and pruritus (1)[70]
Adverse effects: control group	Side effects were reported in 10 patients: upper gastrointestinal bleeding (3), nausea (7), dizziness (2)[70]
Deaths during follow-up period	Non-significant difference between groups. Disease-specific mortality at 6 months 5% in SCS group, 7% in control group; at 2 years 5% and 9% ($p = 0{\cdot}45$), respectively. Kaplan–Meier hazard ratio for the SCS group was 1·09 (95% CI 0·59–2·03)[70]
Pilot study	In a pilot study, 37 patients were randomised, 18 to conservative treatment, 19 to SCS Amputation-free survival at 1 year was 67% in the ESES-treatment group versus 47% in the conservative group At 2 years, amputation-free survival was 61% for SCS, and 39% for control group, non-signficant $p = 0.08$ ($p = 0.082$) with a hazard ratio of 2.3. (most amputations within 1 year after randomisation). Pain relief was significantly better for SCS than control group $p < 0.001$[58]

Table 72 *Critical limb ischaemia: trial results – Suy[73]*

Trial name	Suy[73]
Physical and functional abilities outcome limb salvage rates (details)	Major amputation included transmetatarsal amputation. Defined clinical result as: Excellent: complete relief of ischaemic pain, no limitation of walking distance for daily activities, normal social life, healing of ulcers (if present) or demarcation of gangrene with subsequent healing Good: complete relief of rest pain; however, still some restriction such as toe-amputation, incomplete healing of a painless ulcer and/or incapacitating claudication Unchanged: still analgesic drugs for rest pain, no cure of painful ulcers; deterioration, leading to major amputation
Physical and functional abilities results limb salvage rates: intervention group	Numbers of patients with excellent or good clinical result, at 9 months $n = 15$ out of 20 (75%), at 12 months 13 of 14 remaining patients (93%), at 24 months 8 of 8 remaining patients (100%) Of those 6 patients with major amputation, 1 forefoot amputation, 4 below knee amputation, 1 above knee amputation.
Physical and functional abilities results limb salvage rates: control group	Numbers of patients with excellent or good clinical result, at 9 months $n = 12$ out of 18 (67%), at 12 months 8 of 12 remaining patients (67%), at 24 months 5 of 9 remaining patients (56%) Of those 9 patients with major amputation, 2 forefoot amputation, 5 below knee amputation, 2 above knee amputation.
Physical and functional abilities results limb salvage rates: comparison	Survival curve with end points death without major amputation, or major amputation, non-significant between groups ($p = 0.42$)
Complications and adverse effects outcomes SCS group	Three complications of SCS implantation: 1 infection led to removal and reimplantation of new device, 1 early disconnection requiring surgical connection, 1 late (2 years after operation) broken wire requiring surgical correction
Deaths during follow-up period	Four SCS group; 4 control group. Causes of death (group not specified) 1 mesenteric infarction, 2 cancer, 2 terminal cardiac disease, 1 stroke, 1 cachexia related to refusal of amputation of the contralateral limb, 1 unknown

Table 73 *Critical limb ischaemia: trial results – Jivegard*[74]

Trial name	Jivegard[74]
Pain outcome – VAS (details)	VAS from 0 to 100
Pain results VAS: intervention group	Significant long-term pain relief throughout 18-month follow-up ($p < 0.01$)
Pain results VAS: control group	Significant pain relief at 2-month follow-up ($p < 0.05$), but no significant pain relief at 6-month or 12-month follow-ups (too few observations at 18 months for analysis)
Skin temperature outcome – details	Feeling of warmth (i.e. skin temperature) in the ischaemic area VAS 0 to 100
Skin temperature results: intervention group	Did not significantly change from baseline (both groups)
Skin temperature results: control group	Did not significantly change from baseline (both groups)
Skin temperature results: comparison between groups	No significant difference between groups
Physical and functional abilities outcome – ankle to brachial pressure index (ABI): details	Ankle to brachial index
Physical and functional abilities results ABI: intervention group	No significant changes
Physical and functional abilities results ABI: control group	No significant changes
Physical and functional abilities results ABI: comparison	No significant difference (a non-significant increase in ABI in both groups over 6 months)
Physical and functional abilities outcome – systolic toe to brachial pressure index (STPI): details	Systolic toe to brachial pressure index
Physical and functional abilities results STPI: intervention group	Significantly higher than the baseline value at 2 months and also at 18 months (not at 6 or 12 months)
Physical and functional abilities results STPI: control group	Significantly higher than the baseline value at 2 months (not significant at 6 and 12 months, and too few observations at 18 months for analysis)
Physical and functional abilities results STPI: comparison	No significant difference between the two groups
Physical and functional abilities outcome limb salvage rates (details)	Limb salvage was defined as no amputation, or an amputation on the forefoot only. The extent of amputation was classified in order of increasing handicap as none (no amputation, or minor amputations on the forefoot only), moderate (unilateral below knee amputation), or major (at or above knee level, or any bilateral amputation above ankle level)
Physical and functional abilities results limb salvage rates: intervention group	At 18 months, limb salvage rate 62%, amputations $n = 9$ (36%), numbers of patients with none/moderate/major amputations were 16, 8 and 1, respectively Per treatment analysis at 18 months 69.9% (Subgroup analysis in surviving patients without arterial hypertension, 3/11 amputated. Subgroup analysis in surviving patients with critical limb ischaemia, no amputations in 63%)
Physical and functional abilities results limb salvage rates: control group	At 18 months, limb salvage rate 45%, amputations $n = 14$ (54%), numbers of patients with none/moderate/major amputations were 11, 8 and 6, respectively (Subgroup analysis in surviving patients without arterial hypertension, 9/13 amputated. Subgroup analysis in surviving patients with critical limb ischaemia, no amputations in 33%)

Table 73 *Critical limb ischaemia: trial results – Jivegard[74] (continued)*

Trial name	Jivegard[74]
Physical and functional abilities results limb salvage rates: comparison	No significant difference between groups in limb salvage rates Comparison of none/moderate/major amputations $p = 0.05$ (Subgroup analysis in surviving patients without arterial hypertension, significantly lower amputation rate in SCS group $p = 0.045$. Subgroup analysis in surviving patients with critical limb ischaemia, significantly lower amputation rates in SCS group $p = 0.08$)
Complications and adverse effects outcomes SCS group	One patient underwent reoperation for lead displacement. There were no infections, or other complications
Deaths during follow-up period	Intervention group eight deaths (32%); Control group eight deaths (31%)

Table 74 *Critical limb ischaemia: trial results – Claeys[76]*

Trial name	Claeys[76]
Physical and functional abilities outcome – ankle to brachial pressure index (ABI) (details)	Ankle to brachial pressure index
Physical and functional abilities results ABI: intervention group	At 12 months, increased by 0.03 (+10% on average from baseline) not significant (significant changes in ABI were only observed in SCS patients achieving complete ulcer healing $+0.087 \pm 0.148$, $p < 0.01$)
Physical and functional abilities results ABI: control group	At 12 months, decreased by 0.58 (–17% on average from baseline)
Physical and functional abilities results ABI: comparison	At 12 months, mean change for all SCS patients was significantly different ($p < 0.02$ favouring SCS) from the mean change for all control patients
Physical and functional abilities results limb salvage rates: intervention group	At 12 months minor amputations $n = 6$ (13%); major amputations $n = 7$ (16%) of which 3 above knee, 4 below knee
Physical and functional abilities results limb salvage rates: control group	At 12 months, minor amputations $n = 6$ (15%); major amputations $n = 8$ (20%) of which 1 above knee, 7 below knee
Physical and functional abilities results limb salvage rates: comparison	At 12 months, (most amputations occurred within 3 months of randomisation) not significant between groups for frequency of minor and major amputations
Complications and adverse effects outcomes SCS group	Two lead dislocations and 1 lead break, all corrected
Adverse effects, group not specified	Most common adverse reaction on prostaglandin E1 was minor erythema at site of venous cannulation (15%); hypotension 2.1%, headache 2.8%, flushing 2%, gastrointestinal symptoms 3.2%; no therapy stop due to adverse reactions
Deaths during follow-up period	Non-significant difference between groups SCS 10/45 (22.2%), control group 12/41 (29.3%) $p = 0.07$
Other results	Suggested better response to SCS of patients with $TcPO_2 > 10$ mmHg in terms of ulcer healing

Appendix 5.4: Data extraction: refractory angina

Table 75 *Angina: trial details – deJongste*[79]

Trial name	deJongste[79]
Publication type of main reference (i.e. full report or abstract)	deJongste *et al*., 1994;[79] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, the Netherlands
Power calculation (priori sample calculation)	NR
Primary aim of study	To evaluate efficacy of SCS on exercise capacity and health-related quality of life in patients with intractable angina
Primary study outcome	Exercise capacity, health-related quality of life (daily and social activity scores)
Other study outcomes	Medication use – glyceryl trinitrate intake, angina attacks, electrocardiogram, complications, adverse effects
Intervention (description)	SCS (implanted within 2 weeks of study start)
SCS details (device and implantation)	Permanent implant: either a unipolar Itrel 1 or quadripolar Itrel 2 (Medtronic) implanted pulse generator, electrode either unipolar Pisces Sigma or quadripolar Quad (Medtronic)
Control (description)	No SCS during 8-week study period (then implanted with SCS)

Table 76 *Angina: trial details – ESBY*[82]

Trial name	ESBY[82]
Publication type of main reference (i.e. full report or abstract)	Ekre *et al*., 2002;[82] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, Sweden
Power calculation (priori sample calculation)	NR
Primary aim of study	To investigate whether SCS can be used as an alternative to coronary artery bypass grafting in selected angina patients
Primary study outcome	Angina attacks, medication use – short-acting nitrates, number of patients taking medications
Other study outcomes	Exercise capacity, electrocardiogram, Nottingham Health Profile, Quality of Life Questionnaire Angina Pectoris, complications
Intervention (description)	SCS
SCS details (device and implantation)	Permanent implant: quadripolar electrode, subcutaneous extension lead, implantable pulse generator implanted subcutaneously (Medtronic)
Control (description)	Coronary artery bypass grafting

Table 77 *Angina: trial details – SPiRiT*[83]

Trial name	**SPiRiT**[83]
Publication type of main reference (i.e. full report or abstract)	McNab *et al.*, 2006;[83] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, UK
Power calculation (priori sample calculation)	Sample size required 66 (33 in each group, for exercise treadmill time, assuming minimum clinically significant difference between groups 1.5 min, SD 2 min, two-sided significance of 0.05, 80% power, and 15% dropout)
Primary aim of study	To compare SCS and percutaneous myocardial revascularisation on treadmill exercise time in angina patients
Primary study outcome	Exercise capacity
Other study outcomes	Angina class, Seattle Angina Questionnaire, Short Form 36, complications, adverse effects
Intervention (description)	SCS
SCS details (device and implantation)	Permanent implant: implanted pulse generator Medtronic fully implantable Itrel 3 systems
Control (description)	Percutaneous myocardial laser revascularisation

Table 78 *Angina: trial details – Hautvast*[84]

Trial name	**Hautvast**[84]
Publication type of main reference (i.e. full report or abstract)	Hautvast *et al.*, 1998;[84] full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, the Netherlands
Power calculation (priori sample calculation)	NR
Primary aim of study	To evaluate the efficacy of SCS compared with baseline and control group on exercise capacity in angina patients
Primary study outcome	Exercise capacity
Other study outcomes	Pain VAS, angina attacks, health-related quality of life (linear analogue self assessment), electrocardiogram, complications
Intervention (description)	SCS
SCS details (device and implantation)	Permanent implant: Itrel II (Medtronic) subcutaneously implanted bipolar pulse generator, quadripolar electrode, extension lead.
Control (description)	Inactive spinal cord stimulator implanted, using same procedure as intervention group, inactivated immediately after implantation. (Their device was activated after the 6-week study period)

Table 79 *Angina: trial participants – deJongste*[79]

Trial name	deJongste[79]
Number randomised (total)	17
Number randomised: intervention group	8
Number randomised: control group	9
Number receiving treatment according to allocation: intervention group	8
Number receiving treatment according to allocation: control group	9
Inclusion/exclusion criteria	Inclusion criteria: intractable angina: angiographically documented significant coronary artery disease (maximum 6 months before inclusion), not suitable for revascularisation procedures such as coronary artery bypass grafting or percutaneous transluminal angioplasty; New York Heart Association functional class III or IV angina pectoris; reversible ischaemia documented at least by a symptom-limited treadmill exercise test; and pharmacologically optimal drug treatment for at least 1 month – included maximal tolerated use of at least 2 of the following antianginal medications: long-acting nitrates, beta-adrenergic blocking agents or calcium channel antagonists (medication kept constant throughout study) Exclusion criteria: inability to perform treadmill exercise tests; age over 76; myocardial infarction or unstable angina during last 3 months; somatic disorders of the spine leading to insurmountable technical problems in treatment; significant valve abnormalities demonstrated by a prestudy echocardiographic examination
Characteristics of participants at baseline – intervention group: age	Mean 62.3 years (SD 2.6)
Characteristics of participants at baseline – control group: age	Mean 63.2 years (SD 3.6)
Characteristics of participants at baseline – intervention group: sex	Male 7, female 1
Characteristics of participants at baseline – control group: sex	Male 8, female 1
Characteristics of participants at baseline – intervention group: other	Coronary artery disease (years) 9.8 (SD 0.8) Angina (years) 2.5 (SD 0.2) Myocardial infarction 8 Percutaneous transluminal coronary angioplasty 5 Coronary artery bypass grafting 9 Number of diseased vessels 2.8 Left ventricular ejection fraction 50.2 (SD 11.9) Medication: calcium channel antagonist 8; beta-blocker 7; long-acting nitrates 8; aspirin/coumarin 8
Characteristics of participants at baseline – control group: other	Coronary artery disease (years) 10.9 (SD 1.0) Angina (years) 2.8 (SD 0.3) Myocardial infarction 10 Percutaneous transluminal coronary angioplasty 3 Coronary artery bypass grafting 9 Number of diseased vessels 2.5 Left ventricular ejection fraction 46.5 (SD 13.4) Medication: calcium channel antagonist 9; beta-blocker 6; long-acting nitrates 9; aspirin/coumarin 9

Table 80 *Angina: trial participants – ESBY*[82]

Trial name	ESBY[82]
Number randomised (total)	104
Number randomised: intervention group	53
Number randomised: control group	51
Number receiving treatment according to allocation: intervention group	Permanent implant n=50 (3 had CABG instead due to unstable angina; Mannheimer *et al*., 1998[80])
Number receiving treatment according to allocation: control group	*n* = 49 (1 of these crossed over to SCS after 2 months[80])
Inclusion/exclusion criteria	Inclusion criteria: coronary artery disease, severe angina pectoris, despite optimal pharmacological treatment; coronary artery bypass grafting (CABG) considered possible, ineligible for percutaneous transluminal coronary intervention, no prognostic benefit from surgical revascularisation (includes CABG) (according to ACC/AHA Guidelines 1991). Patient considered intellectually capable of managing the SCS device. No myocardial infarction within the last 6 months Increased, but acceptable according to ACC/AHA, surgical risk [complicated coronary anatomy, previous CABG, low left ventricular ejection fraction (< 40%) in patients with previous CABG, peripheral vascular disease (as a sign of general atherosclerotic disease), diabetes mellitus, renal dysfunction]
Characteristics of participants at baseline – intervention group: age	Mean 72.2 years (range 42–82)
Characteristics of participants at baseline – control group: age	Mean 68.7 years (range 40–81)
Characteristics of participants at baseline – intervention group: sex	Female 12, male 41
Characteristics of participants at baseline – control group: sex	Female 9, male 42
Characteristics of participants at baseline – intervention group: other	Angina class III, *n* = 50 (94%) Angina class IV, *n* = 3 (6%) Mean Higgin's score mean 4·2 (range 0–11) Ejection fraction (EF), mean (range) 0·57 (0·19–0·86) Percentage of patients with EF > 0·4 82% History: Myocardial infarction, *n* = 36 (68%) Cerebrovascular disease, *n* = 11 (21%) Carotid artery stenosis, *n* = 12 (23%) Peripheral vascular disease, *n* = 13 (25%) Renal disease, *n* = 12 (23%) Hypertension, *n* = 23 (43%) Diabetes, *n* = 14 (26%) Current smoking, *n* = 2 (4%) Hyperlipidemia *n* = 8 (15%)

continued

Table 80 *Angina: trial participants – ESBY[82] (continued)*

Trial name	ESBY[82]
	Previous CABG, *n* = 14 (26%)
	One-vessel disease, *n* = 5 (9%)
	Two-vessel disease, *n* = 14 (26%)
	Three-vessel disease, *n* = 34 (64%)
	Complicated anatomy (i.e. peripheral coronary atherosclerosis), *n* = 29 (55%)
Characteristics of participants at baseline – control group: other	Angina class III, *n* = 48 (94%)
	Angina class IV, *n* = 3 (6%)
	Mean Higgin's score 4·1 (range 0–10)
	EF, mean (range) 0·58 (0·26–0·82)
	Percentage of patients with EF > 0·4 83%
	History:
	Myocardial infarction, *n* = 34 (67%)
	Cerebrovascular disease, *n* = 9 (18%)
	Carotid artery stenosis, *n* = 11 (22%)
	Peripheral vascular disease, *n* = 14 (27%)
	Renal disease, *n* = 6 (12%)
	Hypertension, *n* = 19 (37%)
	Diabetes, *n* = 13 (25%)
	Current smoking, *n* = 10 (20%)
	Previous CABG, *n* = 11 (22%)
	Hyperlipidemia *n* = 10 (20%)
	One-vessel disease, *n* = 1 (2%)
	Two-vessel disease, *n* = 10 (20%)
	Three-vessel disease, *n* = 40 (78%)
	Complicated anatomy (peripheral coronary atherosclerosis), *n* = 30 (59%)
Characteristics of participants at baseline – group not indicated	Two of 104 subjects worked full-time, 5 worked part-time, 21 were on sick leave and 76 had retired. The mean Higgin's score (a scoring system for estimation of preoperative risk) was just above 4 and did not differ between the groups. The time from inclusion to operation was on average 1.9 months in the CABG group and 1.0 month in the SCS group ($p < 0.0001$)[80]

Table 81 *Angina: trial participants – SPiRiT*[83]

Trial name	SPiRiT[83]
Number randomised (total)	68
Number randomised: intervention group	34
Number randomised: control group	34
Number receiving treatment according to allocation: intervention group	32 (1 refused, 1 had control treatment)
Number receiving treatment according to allocation: control group	33 (1 refused)
Inclusion/exclusion criteria	Inclusion criteria: Canadian Cardiovascular Society (CCS) class 3/4 angina and reversible perfusion defects; limiting angina despite maximally tolerated anti-angina medication; angiographically documented coronary disease unsuitable for conventional revascularisation (this judgement was made by a consultant interventional cardiologist in conjunction with the referring consultant cardiologist/cardiothoracic surgeon); and reversible ischaemia on 99m sestamibi-technetium scanning Exclusion criteria: myocardial wall thickness < 8 mm in the areas to be treated by percutaneous myocardial revascularisation; implanted pacemakers or defibrillators; or co-morbidity that was considered by the assessing clinician to be of greater significance than angina pectoris.
Characteristics of participants at baseline – intervention group: age	Mean 64.2 years (SD 7.3)
Characteristics of participants at baseline – control group: age	Mean 62.9 years (SD 9.6)
Characteristics of participants at baseline – intervention group: sex	Female 5; male 29
Characteristics of participants at baseline – control group: sex	Female 3; male 31
Characteristics of participants at baseline – intervention group: other	Previous revascularisation: percutaneous transluminal coronary angioplasty (PTCA) *n* = 6 (18%); stents *n* = 6 (18%); coronary artery bypass grafting (CABG) *n* = 32 (94%) Exercise tolerance test: total exercise time, mean (SD) 6.38 (3.45); time to angina, mean (SEM) (calculated from Kaplan–Meier time to angina curves because some patients stopped exercising before onset of angina) 4.68 (0.52); no angina during exercise 7 (21%) CCS class at baseline 2 0 (0%), 3 22 (65%), 4 12 (35%) Short Form 36: Aggregate physical score, mean (SD) 21.1 (10.8); Aggregate mental score, mean (SD) 34.1 (13.1) Seattle Angina Questionnaire: Exertional capacity scale, mean (SD) 62.9 (27.3); Angina stability scale, mean (SD) 40.4 (17.4); Angina frequency scale, mean (SD) 28.2 (20.5); Treatment satisfaction scale, mean (SD) 80.5 (15.7); Disease perception scale, mean (SD) 35.8 (22.1) EuroQoL EQ5D, mean (SD) 0.41 (0.33)

continued

Table 81 *Angina: trial participants – SPiRiT[83] (continued)*

Trial name	SPiRiT[83]
Characteristics of participants at baseline – control group: other	Previous revascularisation: PTCA *n* = 10 (29%); stents *n* = 6 (18%); CABG *n* = 32 (94%) Exercise tolerance test: total exercise time, mean (SD) 7.41 (3.68); time to angina, mean (SEM) (calculated from Kaplan–Meier time to angina curves because some patients stopped exercising before onset of angina) 5.47 (0.68); no angina during exercise 7 (21%) CCS class at baseline 2 0 (0%), 3 25 (74%), 4 9 (26%) Short Form 36: Aggregate physical score, mean (SD) 19.8 (10.3); Aggregate mental score, mean (SD) 32.2 (12.0) Seattle Angina Questionnaire: Exertional capacity scale, mean (SD) 66.9 (27.2); Angina stability scale, mean (SD) 44.9 (16.0); Angina frequency scale, mean (SD) 24.4 (16.2); Treatment satisfaction scale, mean (SD) 73.0 (17.5); Disease perception scale, mean (SD) 36.3 (18.6) EuroQoL EQ5D, mean (SD) 0.48 (0.27)

Table 82 *Angina: trial participants – Hautvast*[84]

Trial name	Hautvast[84]
Number randomised (total)	25
Number randomised: intervention group	13
Number randomised: control group	12
Number receiving treatment according to allocation: intervention group	13
Number receiving treatment according to allocation: control group	12
Inclusion/exclusion criteria	Inclusion criteria: chronic intractable angina pectoris class III or IV according to the New York Heart Association, despite maximal tolerated dosage of beta-blocking agents, calcium antagonists, and long-acting nitrates; ineligible for percutaneous transluminal coronary angioplasty or coronary artery bypass grafting Exclusion criteria: inability to perform an exercise test; cardiac conduction disturbances disabling recognition of ischaemia on the electrocardiogram; and the anatomic inability to accept stimulator implantation; aged over 75 years; left ventricular ejection fraction < 30%
Characteristics of participants at baseline – intervention group: age	Mean age 62 years (SD 8)
Characteristics of participants at baseline – control group: age	Mean age 63 years (SD 7)
Characteristics of participants at baseline – intervention group: sex	Female 7; male 6
Characteristics of participants at baseline – control group: sex	Female 4; male 8
Characteristics of participants at baseline – intervention group: other	History of coronary artery disease (years) mean 9 (SD 4) Left ventricular ejection fraction (%) mean 56 (SD 10) Number of of stenosed coronary arteries mean 2.1 (SD 0.6) Total myocardial infarctions *n* = 6 Total coronary bypass surgeries *n* = 10 Total coronary angioplasties *n* = 12 Medication: beta-blockers *n* = 12; Calcium re-entry blockers *n* = 13; Long-acting nitrates *n* = 12
Characteristics of participants at baseline – control group: other	History of coronary artery disease (years) mean 11 (SD 5) Left ventricular ejection fraction (%) mean 52 (SD 12) Number of stenosed coronary arteries mean 2.5 (SD 0.5) Total myocardial infarctions *n* = 11 Total coronary bypass surgeries *n* = 13 Total coronary angioplasties *n* = 3 Medication: beta-blockers *n* = 11; Calcium re-entry blockers *n* = 11; Long-acting nitrates *n* = 12

Table 83 *Angina: trial results – deJongste*[79]

Trial name	deJongste[79]
Medication use outcome – details	Amount of sublingual glyceryl trinitrate (GTN) intake, registered in a diary during 2 weeks, both at baseline and during weeks 6–8
Medication use results: intervention group	GTN per week median baseline 13.3 (95% CI 8.8–17.7), 6–8 weeks 1.6 (0.3–6.9), significant reduction from baseline $p < 0.004$
Medication use results: control group	GTN per week median baseline 8.3 (95% CI 3.3–32.6), 6–8 weeks 8.5 (2.8–27.1)
Medication use results: comparison between groups	GTN per week significant difference between SCS and control groups in change from baseline $p < 0.05$
Physical and functional abilities outcome – rest angina episodes/ angina attacks/angina class	Number of angina pectoris attacks registered in a diary during 2 weeks, both at baseline and during weeks 6–8
Physical and functional abilities results angina: intervention group	Angina pectoris per week median baseline 16.6 (95% CI 11.4–26.1), 6–8 weeks 9.0 (4.0–14.2) significant improvement from baseline $p < 0.003$
Physical and functional abilities results angina: control group	Angina pectoris per week median baseline 16.5 (95% CI 9.0–23.9), 6–8 weeks 13.6 (7.7–20.8)
Physical and functional abilities results angina: comparison	Angina pectoris per week significant difference change from baseline SCS vs control group $p < 0.05$
Physical and functional abilities outcome – electrocardiograph	Left ventricular ejection fraction (LVEF), 24-hour electrocardiogram (ECG)
Physical and functional abilities electrocardiograph results: intervention group	No change from baseline on LVEF (baseline 48.2 ± 2.9%, 6–8 weeks 47.1 ± 3.2%), no change on mean values of average minimal or maximal heart rate during 24-hour ambulatory ECGs
Physical and functional abilities outcome – exercise capacity	At baseline and after 6–8 weeks, two exercise tests were performed at an interval of at least 1 week. Exercise tests performed with active spinal cord stimulation during exercise. Exercise on Quinton Q55 treadmill ergometer, with gradually increasing workloads. Patients subjective scale, 0 = no angina to 3 = unbearable pain, at level 3 exercise was stopped, end points angina pain, fatigue, shortness of breath, onset of threatening arrhythmia or exertional hypotension
Physical and functional abilities results exercise capacity: intervention group	Exercise duration (seconds) mean (SE) baseline 659 (± 121), 6–8 weeks 827 (± 138), significant change from baseline $p < 0.05$. Rate-pressure product (beats/min × mmHg × 10^{-3}) baseline mean (SE) 12.9 (± 0.75), 6–8 weeks 13.8 (± 1.3), significant change from baseline $p < 0.05$. Time to angina (seconds) mean (SE) baseline 520 (± 138), 6–8 weeks 691 (± 174), significant change from baseline $p < 0.05$. Heart rate at maximal exercise (beats/min) mean (SE) baseline 90.1 (± 5.1), 6–8 weeks 91.8 (± 4.4). Systolic blood pressure at maximal exercise (mmHg) mean (SE) baseline 139.8 (± 3.4), 6–8 weeks 152.9 (± 7.0), significant change from baseline $p < 0.05$. ST depression at maximal exercise (mV) mean (SE) baseline 0.09 (± 0.01), 6–8 weeks 0.05(± 0.02), significant change from baseline $p < 0.05$
Physical and functional abilities results exercise capacity: control group	Exercise duration (seconds) mean (SE) baseline 705 (± 136); 6–8 weeks 694 (± 67). rate-pressure product (beats/min × mmHg × 10^{-3}) baseline mean (SE) 14.8 (± 9.1), 6–8 weeks 14.2 (± 13.9). Time to angina (seconds) mean (SE) baseline 380 (± 78), 6–8 weeks 438 (± 91). Heart rate at maximal exercise (beats/min) mean (SE) baseline 97.7 (± 8.1), 6–8 weeks 97.9 (± 7.2). Systolic blood pressure at maximal exercise (mmHg) mean (SE) baseline 148.7 (± 6.3), 6–8 weeks 144.5 (± 6.2). ST depression at maximal exercise (mV) mean (SE) baseline 0.13 (± 0.03), 6–8 weeks 0.11 (± 0.02).
Physical and functional abilities results exercise capacity: comparison	Exercise duration significant difference between change in SCS group vs change in control group $p < 0.03$. ST depression at maximal exercise significant difference between change in SCS group and change in control group $p < 0.02$. Time to angina significant difference between change in SCS group and change in control group $p < 0.05$. Other variables not significant between groups
Health-related quality of life outcome Daily activities (details)	Scoring of daily activity (physical exercise) and social activities was assessed by validated standardised questionnaire at baseline and at week 8

Table 83 *Angina: trial results – deJongste[79] (continued)*

Trial name	deJongste[79]
Health-related quality of life results Daily activities: intervention group	Daily activity score (ADL) baseline median 1.37 (95% CI 1.15–1.67), 6–8 weeks 2.06 (1.65–2.26) significantly improved from baseline $p < 0.008$
	Social activity score (SAS) median baseline 1.28 (95% CI 0.99–1.69), 6–8 weeks 2.10 (1.61–2.44) sig improvement from baseline $p < 0.005$
Health-related quality of life results Daily activities: control group	Daily activity score (ADL) baseline median 1.24 (95% CI 1.06–1.50), 6–8 weeks 1.25 (1.10–1.71)
	Social activity score (SAS) median baseline 1.30 (95% CI 0.60–2.00), 6–8 weeks 1.39 (1.10–1.65)
Health-related quality of life results Daily activities: comparison	Daily activity score (ADL) significant difference between change in SCS group and change in control group $p < 0.05$
	Social activity score significant difference between change in SCS group and change in control group $p < 0.05$
Complications and adverse effects outcomes SCS group	No adverse events during the 6–8 week study period

Table 84 *Angina: trial results – ESBY*[82]

Trial name	ESBY[82]
Medication use outcome – details	Numbers of patients taking particular drug, at baseline and 6 month follow-up. Short-acting nitrate consumption[80]
Medication use results: intervention group	Significant reduction ($p < 0.0001$) in short-acting nitrates at 6 months, no other significant differences. Number of patients taking drug at baseline and at 6 months, respectively:
	Short-acting nitrates 47, 21
	Long-acting nitrates 39, 36
	Beta-blockers 48, 43
	Calcium blockers 21, 20
	ACE inhibitors 9, 7
	Aspirin 46, 42
	Anticoagulants 4, 4
	Diuretics 16, 15
	Digoxin 3, 3
	Lipid-lowering agents 6, 6
	Oral antidiabetics 6, 6
	Insulin 4, 3
	Mean number of drugs taken daily, per patient 4·8, 4·9
	Nitrate consumption, doses/week baseline 15.2 (18.8) 6-month follow-up 4.1 (10.5) significant reduction from baseline $p < 0.0001$[80]
Medication use results: control group	Significant reduction in short-acting nitrates ($p < 0.0001$), long-acting nitrates ($p < 0.0001$), beta-blockers ($p < 0.001$), calcium blockers ($p < 0.01$), and mean number of drugs taken daily ($p < 0.0001$) at 6 months, no other significant differences. Number of patients taking drug at baseline and at 6 months, respectively:
	Short-acting nitrates 47, 13
	Long-acting nitrates 43, 8
	Beta-blockers 43, 24
	Calcium blockers 25, 8
	ACE inhibitors 8, 8
	Aspirin 42, 33
	Anticoagulants 3, 2
	Diuretics 12, 10
	Digoxin 1, 4
	Lipid-lowering agents 4, 3
	Oral antidiabetics 5, 2
	Insulin 6, 7
	Mean number of drugs taken daily, per patient 4.2, 3.1
	Nitrate consumption, doses/week baseline 13.7 (12.1) 6-month follow-up 3.1 (8.7) significant reduction from baseline $p < 0.0001$[80]

Table 84 *Angina: trial results – ESBY[82] (continued)*

Trial name	ESBY[82]
Medication use results: comparison between groups	There was significantly more reduction for coronary artery bypass grafting (CABG) (than SCS) for long-acting nitrates ($p < 0.0001$), beta-blockers ($p < 0.01$), calcium blockers ($p < 0.05$), and mean number of drugs taken daily per patient ($p < 0.0001$)
	Non-significant differences between groups for consumption of short-acting nitrates[80]
Physical and functional abilities outcome – rest angina episodes/ angina attacks/angina class	Clinical outcome was recorded on a questionnaire given to the patient shortly after the exercise tests. Patients reported their frequency of angina attacks and consumption of short-acting nitrates per week
	At follow-up, the subjective treatment effect was recorded with the use of a scale ranging from 1 (better or free from symptoms) to 2 (unchanged or worse)[80]
Physical and functional abilities results angina: intervention group	83.7% had a good self-estimated treatment effect (better or symptom free). Angina attack frequency, attacks/week baseline mean 14.6 (SD 13.5), follow-up mean 4.4 (SD 7.4) significant reduction $p < 0.0001$[80]
Physical and functional abilities results angina: control group	79.5% had a good self-estimated treatment effect. Angina attack frequency, attacks/week baseline mean 16.2 (SD 12.6) follow-up mean 5.2 (SD 10.3) significant reduction $p < 0.0001$[80]
Physical and functional abilities results angina: comparison	Non-significant difference between groups for self-estimated treatment effect, or for frequency of angina attacks[80]
Physical and functional abilities outcome – electrocardiograph	Holter electrocardiogram (ECG): 24-hr ambulatory ECG at baseline and 6 months SCS group had stimulation discontinued 24 hours before and during ECG monitoring. Angina attacks recorded in diary during monitoring. ST analysis – patients with left bundle branch block, left ventricular hypertrophy, digitalis medication, atrial fibrillation and pacemaker were excluded[81]
Physical and functional abilities electrocardiograph results: intervention group	At 6 months number and duration of ischaemic episodes unchanged, ($n = 39$); ischaemic duration (minutes) mean baseline 392.5 (SD 511.4), follow-up 419.9 (SD 506.9); ischaemic episodes mean baseline 28.4 (SD 32.1), follow-up 29.1 (SD 30.8); ischaemic burden mean baseline 22.7 (SD 39.3), follow-up 44.2 (SD 124.2)
	Number of angina attacks decreased ($p < 0.02$) ($n = 49$) mean baseline 1.5 (SD 2.1), follow-up 0.7 (SD1.3)
	Resting ECG ($n = 43$) QRS duration (ms) mean baseline 94.6 (SD 12.6), follow-up 97.3 (SD 13.4); left ventricular hypertrophy index (mm) mean baseline 13.3 (SD 6.4), follow-up 13.1 (SD6.3); myocardial infarction score mean baseline 1.0 (SD 1.1), follow-up 1.1 (SD 1.1)
	Heart frequency ($n = 48$) (beats per minute) mean baseline 66.5 (SD 9.8), follow-up 64.9 (SD 9.4); heart rate variability (ms) mean baseline 545.0 (SD 184.0), follow-up 540.6 (SD 192.5)[80]
Physical and functional abilities electrocardiograph results: control group	Number and duration of ischaemic episodes decreased ($n = 30$) ischaemic duration (minutes) mean baseline 426.5 (SD 495.3), follow-up 212.8 (SD 420.8); ischaemic episodes mean baseline 35.2 (SD 39.9), follow-up 17.8 (SD 21.4); ischaemic burden mean baseline 47.6 (SD 124.6), follow-up 23.8 (SD 78.5)
	Number of angina attacks decreased (for both groups together $p = 0.0001$), control group ($n = 36$) mean baseline 2.1 (SD 2.2), follow-up 0.5 (SD 1.3)
	Resting ECG ($n = 29$) QRS duration (ms) mean baseline 97.2 (SD 13.1), follow-up 98.5 (SD 15.0); left ventricular hypertrophy index (mm) mean baseline 13.1 (SD 5.7), follow-up 15.4 (SD 5.8); myocardial infarction score mean baseline 1.2 (SD 1.3), follow-up 1.5 (SD 1.3)
	Heart frequency ($n = 35$) (beats per minute) mean baseline 66.5 (SD 8.1), follow-up 72.4 (SD 10.6); heart rate variability (ms) mean baseline 542.6 (SD 125.7), follow-up 464.3 (SD 176.7)[80]

continued

Table 84 *Angina: trial results – ESBY[82] (continued)*

Trial name	ESBY[82]
Physical and functional abilities electrocardiograph results: comparison	SCS significantly greater number ($p < 0.05$) and longer duration ($p = 0.02$) of ischaemic episodes than control
	Non-significant between groups for number of angina attacks
	Non-significant difference between groups for QRS duration, myocardial Infarction score, heart rate variability. Left ventricular hypertrophy index increased only in control group ($p < 0.01$)
	Heart frequency was lower in the SCS group than the control group ($p = 0.0001$)[80]
Physical and functional abilities outcome – exercise capacity	At baseline and 6 months with a 12-lead ECG on a bicycle ergometer
	Blood pressure, heart rate and ECG changes recorded at each level. Exercise stopped when patient experienced maximum effort, chest pain rated 6 to 7 of 10 on the Borg scale or dyspnoea rated 6 to 7 of 10, or showed signs of severe myocardial ischaemia or hypotension
	Patients randomised to SCS had stimulation treatment discontinued 24 hours before the second exercise test[80]
	(Unlike other trials, SCS was switched off during testing. The authors of this trial had previously conducted a case series of angina patients which they had shown that SCS could increase tolerance to pacing[103])
Physical and functional abilities results exercise capacity: intervention group	Exercise test results (mean and SD) at baseline and 6-month follow-up:
	Maximum workload capacity, W 90.6 (29.2), 92.2 (33.7) non-significant difference from baseline
	ST-segment depression on maximum workload, mm –22.01 (1.17), –21.95 (1.18) non-significant difference from baseline
	ST-segment depression on comparable workload, mm –21.73 (1.14), –21.66 (1.24) non-significant difference from baseline
	Rate pressure product (RPP) on maximum workload, mmHg/min × 10^3 21.4 (5.8), 21.2 (6.9) non-significant difference from baseline
	RPP on comparable workload, mmHg/min × 10^3 20.9 (5.7), 20.6 (6.5) non-significant difference from baseline[80]
Physical and functional abilities results exercise capacity: control group	Exercise test results (mean and SD) at baseline and 6 month follow-up:
	Maximum workload capacity, W 86.2 (23.1) 99.0 (28.0) significant increase $p = 0.002$
	ST-segment depression on maximum workload, mm –21.46 (1.36), –20.68 (1.52) significant reduction $p = 0.0009$
	ST-segment depression on comparable workload, mm –21.40 (1.39), –20.46 (1.13) significant reduction $p = 0.0001$
	RPP on maximum workload, mmHg/min × 10^3 21.6 (5.4), 25.4 (5.6) significant increase $p = 0.0001$
	RPP on comparable workload, mm Hg/min × 10^3 21.3 (5.4), 23.0 (5.4) significant increase $p = 0.034$[80]
Physical and functional abilities results exercise capacity: comparison	At 6 months, the control group had an increase in exercise capacity ($p = 0.02$) and less ST-segment depression on maximum ($p = 0.005$) and comparable ($p = 0.0009$) workloads than the SCS group
	The rate-pressure products on maximum ($p = 0.0003$) and comparable ($p = 0.03$) workloads were higher for control than for SCS group[80]
Health-related quality of life outcome Nottingham health profile (details)	Nottingham Health Profile two parts

Table 84 *Angina: trial results – ESBY[82] (continued)*

Trial name	ESBY[82]
Health-related quality of life results Nottingham health profile: intervention group	In both quality of life assessments there were significant improvements 6 months after SCS/CABG compared to run-in ($p < 0{\cdot}001$), and the results were consistent after 58 months
	Significant improvements in 'energy' and 'pain' scores, The magnitude of improvement in NHP total score was > 30%
	(Estimated from figure NHP part 1 baseline 24; 6 months 16; 4.8 years 18. NHP part 2 baseline 34; 6 months 24; 4.8 years 29)
Health-related quality of life results Nottingham health profile: control group	In both quality of life assessments there were significant improvements 6 months after SCS/CABG compared to run-in ($p < 0{\cdot}001$), and the results were consistent after 58 months
	Significant improvements in 'energy' and 'pain' scores, magnitude of improvement in NHP total score was > 30%
	(Estimated from figure NHP part 1 baseline 26; 6 months 18; 4.8 years 19. NHP part 2 baseline 40; 6 months 25; 4.8 years 29)
Health-related quality of life results Nottingham health profile: comparison	There were no significant differences between the CABG and the SCS groups, at either baseline or after the procedure (6 months and 58 months) in any subcategory of NHP. Both groups reached a level comparable to that of a healthy population at the corresponding age
Health-related quality of life Quality of life questionnaire Angina Pectoris QLQ-AP details	Quality of life questionnaire Angina Pectoris (QLQ-AP), a disease-specific questionnaire
Health-related quality of life results QLQ-AP: intervention group	Significant improvements 6 months after SCS compared to run-in ($p < 0{\cdot}001$), and the results were consistent after 4·8 years. Significant improvements in all four subcategories
Health-related quality of life results QLQ-AP: control group	Significant improvements 6 months after CABG compared to run-in ($p < 0{\cdot}001$), and the results were consistent after 4·8 years. Significant improvements in all four subcategories
Health-related quality of life results QLQ-AP: comparison	At 6 months and 58 months, non-significant between groups
Complications and adverse effects outcomes SCS group	During the follow-up, three patients had their spinal cord electrodes surgically corrected. The stimulator had to be removed because of infection in one patient
Morbidity	SCS fewer hospitalisation days in connection with intervention ($p < 0.0001$) and cardiac morbidity ($p < 0.05$) than control group
	Cardiac events did not differ between the groups. Eight cerebrovascular events in the CABG group and 2 in SCS group. This difference in cerebrovascular morbidity was statistically significant ($p = 0.03$). Three patients in the CABG group and 2 patients in the SCS group had both cardiac and cerebrovascular events. Total cardiac and cerebrovascular morbidity (including patients who had one or more fatal or non-fatal cardiac or cerebrovascular event) was 14 patients in the CABG group and 8 in the SCS group, which was not statistically significant ($p = 0.08$)[80]
Deaths during follow-up period	At 6 months, 1 patient in the SCS group and 7 patients in the CABG group died which was significant ($p < 0{\cdot}02$); however, 3 of the deaths in the CABG group had occurred before surgery. At 3 and 5 years, there were no significant differences between the groups. Three years after randomisation, 45 of 53 patients (84·9%) were alive in the SCS group, and 39 of 51 (76·5%) in the CABG group. After 5 years, 40 of 53 patients (75·5%) were alive in the SCS group, and 35 of 51 (68·6%) in the CABG group. Sixty-six per cent of the deaths were cardiac deaths, without significant difference between the groups

continued

Table 85 *Angina: trial results – SPiRiT*[83]

Trial name	SPiRiT[83]
Physical and functional abilities outcome – rest angina episodes/ angina attacks/angina class	Angina class as measured by the Canadian Cardiovascular Society (CCS) angina scale
Physical and functional abilities results angina: intervention group	At 12 months ($n = 30$), change in CCS of 2 or more classes: No 19 (63%) Yes 11 (37%)
Physical and functional abilities results angina: control group	At 12 months ($n = 30$), change in CCS of 2 or more classes: No 24 (80%) Yes 6 (20%)
Physical and functional abilities results angina: comparison	Analysis: treating deaths and dropouts as failures would reduce the success rate to 12/34 (35%) in the SCS group and 5/34 (15%) in the percutaneous myocardial revascularisation (PMR) group at 3 months ($p = 0.093$) and to 11/34 (32%) and 6/34 (15%) at 12 months ($p = 0.263$) Analysis excluding patients without follow-up: When viewed as a trend, the change in CCS score at 3 months was significantly greater for SCS patients ($p = 0.018$). This trend continued to 12 months, with SCS patients having greater improvement in CCS class ($p = 0.042$)
Physical and functional abilities outcome – exercise capacity	Total exercise time on a modified Bruce protocol exercise tolerance test. All tests terminated by the patient For subjects with a spinal cord stimulator, the device was on for the purposes of the tests except for one subject at 3 months and two at 12 months in whom the device was switched off for technical reasons
Physical and functional abilities results exercise capacity: intervention group	The increase in angina-free exercise time over baseline was significant for both groups Exercise tolerance at 3 months ($n = 32$) Total exercise time, mean (SEM) 7.33 (0.62) Time to angina, mean (SEM) (calculated from area under the Kaplan–Meier time to angina curves because some patients stopped exercising before onset of angina) 7.31 (0.73) No angina during exercise 10 (31%) Exercise tolerance at 12 months ($n = 30$) Total exercise time, mean (SEM) 7.08 (0.67) Time to angina, mean (SEM) 7.30 (0.90) No angina during exercise 11 (37%)
Physical and functional abilities results exercise capacity: control group	The increase in angina-free exercise time over baseline was significant for both groups Exercise tolerance at 3 months ($n = 33$) Total exercise time, mean (SEM) 7.32 (0.66) Time to angina, mean (SEM) 6.26 (0.65) No angina during exercise 7 (21%) Exercise tolerance at 12 months ($n = 30$) Total exercise time, mean (SEM) 7.12 (0.71) Time to angina, mean (SEM) 6.86 (0.82) No angina during exercise 10 (33%)

Table 85 *Angina: trial results – SPiRiT[83] (continued)*

Trial name	SPiRiT[83]
Physical and functional abilities results exercise capacity: comparison	The mean total exercise time at 3 months was almost identical in the two groups (mean difference 0.01 min, 95% CI 21.75–1.78, $p + 0.989$). Adjusting for baseline, the difference between the groups was 0.61 min (95% CI 20.55–1.77, $p = 0.353$) The mean total exercise time at 12 months remained very similar in the two groups (mean difference 20.04 min, 95% CI 21.94–1.86, $p = 0.970$). Adjusting for baseline, the difference in total exercise time between groups was 0.59 min (95% CI 21.02–2.20, $p = 0.466$). At 3 months, mean time to onset of angina increased significantly from baseline in the SCS group (2.63 ± 0.58 vs 0.79 ± 0.61 min in the PMR group) with a difference between the two groups at 3 months of 1.84 min (95% CI 0.19–3.49 min, $p = 0.028$) At 12 months there was no significant difference between the two groups for increase in angina-free exercise time 1.23 min (95% CI 20.61–3.07 min, $p = 0.191$)
Health-related quality of life SF36 details	The generic Short Form 36 – mental component score and physical component score
Health-related quality of life results SF36: intervention group	Some improvements at 3 and 12 months (non-significant)
Health-related quality of life results SF36: control group	Some improvements at 3 and 12 months (non-significant)
Health-related quality of life results SF36: comparison	Non-significant difference between groups
Health-related quality of life Seattle angina questionnaire details	Disease-specific Seattle Angina Questionnaire
Health-related quality of life results Seattle angina questionnaire: intervention group	Some improvements at 3 and 12 months (non-significant)
Health-related quality of life results Seattle angina questionnaire: control group	Some improvements at 3 and 12 months (non-significant)
Health-related quality of life results Seattle angina questionnaire: comparison	Non-significant difference between groups
Complications and adverse effects outcomes SCS group	There were no complications associated with implant of SCS device, but one subject reported a change in distribution of paraesthesia on the day following the implant procedure. For this subject, migration of the epidural lead was reported and a replacement lead was inserted 2 months after the initial procedure Fifty-seven events occurred in 20 patients in the SCS group, with 26 events categorised as being related to the SCS procedure. The majority of these (18 events) were an undesirable change in the level of stimulation (which could be resolved by reprogramming in 13 cases or by repositioning or replacing the lead in 5 cases), other events were pain at neurostimulator site and neurostimulator generator migration A further 30 events in the SCS group were categorized as unrelated to the procedure; most were related to the underlying disease. Of the adverse events 41 were classed as severe.
Adverse effects: control group	Surgery: 1 procedural complication was reported, a femoral pseudoaneurysm, which resolved within 24 hours Follow-up: 26 adverse events were reported by 15 patients in the control group Four events were related to the PMR procedure, one of which occurred in a patient randomized to SCS. A further 23 events in the control group were categorised as unrelated to the procedure; most were related to the underlying disease. Of the adverse events 24 were classed as severe

continued

Table 85 *Angina: trial results – SPiRiT[83] (continued)*

Trial name	SPiRiT[83]
Complications and adverse effects: comparison	The SCS group reported significantly more adverse events than the PMR group ($p = 0.001$)
	There was no significant difference between groups in adverse events categorised as unrelated to the procedure ($p = 0.342$), or the subset of these which were disease-related ($p = 0.077$)
	The SCS group had significantly more severe adverse events ($p = 0.039$), classed as such because they either required admission, prolonged stay in hospital, required surgery, were life-threatening or ultimately resulted in death
Deaths during follow-up period	Six deaths: four in the SCS group (ischaemic heart disease, metastatic squamous cell carcinoma, presumed malignancy, and acute myocardial infarction)
	Two deaths in control group (stomach carcinoma, and ischaemic heart disease/myocardial infarction)

Table 86 *Angina: trial results – Hautvast*[84]

Trial name	Hautvast[84]
Pain outcome – VAS (details)	VAS 0–10 cm, 2 weeks before the first baseline tests and during the last 2 weeks of study (6 weeks follow-up), patients were instructed to record each day
Pain results VAS: intervention group	VAS (cm) baseline 3.7 ± 2.0, 6 weeks 2.6 ± 1.4, difference (%) –25 ± 52 significantly different from baseline $p = 0.03$
Pain results VAS: control group	VAS (cm) baseline 3.4 ± 1.6, 6 weeks 3.2 ± 1.4, difference (%) – 1 ± 30
Pain results VAS: comparison between groups	Non-significant difference between groups
Medication use outcome – details	Patient diary: 2 weeks before the first baseline tests and during the last 2 weeks of study, patients were instructed to record use of sublingual nitrate tablets
Medication use results: intervention group	Nitrogen consumption (tablets): baseline 3.6 ± 2.8, 6 weeks 1.6 ± 2.2; difference (%) –48 ± 49 significantly different from baseline $p = 0.01$
Medication use results: control group	Nitrogen consumption (tablets): baseline 2.3 ± 1.6, 6 weeks 2.6 ± 1.7; difference(%) 27 ± 63
Medication use results: comparison between groups	After 6 weeks of treatment, there was a decrease of consumption of sublingual nitrate tablets ($p = 0.03$) in comparison with control subjects
Physical and functional abilities outcome – rest angina episodes/ angina attacks/angina class	Patient diary: 2 weeks before the first baseline tests and during the last 2 weeks of study, patients were instructed to record each day the number of angina attacks in a diary before the treadmill tests
Physical and functional abilities results angina: intervention group	Angina attacks (per day): baseline 4.3 ± 2.4, 6 weeks 2.3 ± 1.9; difference(%) –41 ± 44 significantly different from baseline $p = 0.01$
Physical and functional abilities results angina: control group	Angina attacks (per day): baseline 2.9 ± 1.4, 6 weeks 3.2 ± 1.5; difference (%) 33 ± 82
Physical and functional abilities results angina: comparison	After 6 weeks of treatment, there was a decrease of angina attacks ($p = 0.01$) in comparison with control subjects
Physical and functional abilities outcome – electrocardiograph	48-hour ambulatory electrocardiographic monitoring At baseline, after the treadmill test was taken but before implantation of the stimulator, a 48-hour ambulatory electrocardiographic recording was made. This recording was repeated after 6 weeks of study
Physical and functional abilities electrocardiograph results: intervention group	Number of ischaemic episodes (median and range): baseline 3.0 (0–23), 6 weeks 0.0 (0–12); difference (%) –3.0 (–17 to – 1) significantly different from baseline $p = 0.01$ Total duration of ischaemia (minutes, median and range): baseline 12.8 (0–72.3), 6 weeks 0.0 (0–55.9); difference (%) – 10.1 (–54.9 to –8.5) significantly different from baseline $p = 0.01$ Total ischaemic burden (mm × min, median and range): baseline 22.2 (0–1583), 6 weeks 0.0 (0–123.8); difference (%) – 19.4 (–1555.8 to – 19.8) significantly different from baseline $p = 0.01$ At baseline, nine subjects in the treatment group had ischaemic episodes on the 48-hour electrocardiogram. One patient in the treatment group had no ischaemic episodes both at baseline and after 6 weeks
Physical and functional abilities electrocardiograph results: control group	Number of ischaemic episodes (median and range): baseline 0.5 (0–27), 6 weeks 1.0 (0–14); difference (%) 0.0 (–22 to –8) Total duration of ischaemia (minutes, median and range): baseline 1.2 (0–152.6), 6 weeks 1.9 (0–127.1); difference (%) 0.2 (–87 to –96.2) Total ischaemic burden (mm × min, median and range): baseline 1.2 (0–589), 6 weeks 2.7 (0–244.8); difference (%) 0.3 (–589 to – 197.8) At baseline, six patients in the control group had ischaemic episodes on the 48-hour electrocardiogram. Three patients in the control group had no ischaemic episodes either at baseline or after 6 weeks

continued

Table 86 *Angina: trial results – Hautvast[84] (continued)*

Trial name	Hautvast[84]
Physical and functional abilities electrocardiograph results: comparison	Number of ischaemic episodes significantly different between groups $p = 0.04$. Non-significant difference between duration and burden
Physical and functional abilities outcome – exercise capacity	Exercise capacity and concomitant time to onset of angina pain, assessed with symptom-limited treadmill exercise
	Criteria for discontinuation were unbearable angina pain, exhaustion, onset of threatening arrhythmia, or exertional hypotension
	For subjects within the SCS group, the device was on for the purposes of the tests
Physical and functional abilities results exercise capacity: intervention group	Treadmill exercise tests:
	Time to angina (seconds): baseline 250 ± 67, 6 weeks 319 ± 85; difference (%) 39 ± 59, significantly different from baseline $p = 0.03$
	Total exercise duration (seconds): baseline 453 ± 156, 6 weeks 533 ± 184; difference (%) 19 ± 24 significantly different from baseline $p = 0.03$
	ST-segment depression at maximal exercise (mV): baseline 0.16 ± 0.06, 6 weeks 0.13 ± 0.07; difference (%) –12 ± 51
	Rate-pressure product at maximal exercise (mmHg × 100/min): baseline 163 ± 47, 6 weeks 178 ± 60; difference (%) 12 ± 31
	ST-segment depression at comparable workload (mV): baseline 0.15 ± 0.07, 6 weeks 0.11 ± 0.06; difference (%) –26 ± 39 significantly different from baseline $p = 0.04$
	Rate-pressure product at comparable workload (mmHg × 100/min): baseline 161 ± 48, 6 weeks 150 ± 57; difference (%) –3 ± 37
Physical and functional abilities results exercise capacity: control group	Treadmill exercise tests:
	Time to angina (seconds): baseline 287 ± 119, 6 weeks 246 ± 97; difference (%) –9 ± 21
	Total exercise duration (seconds): baseline 447 ± 214, 6 weeks 427 ± 177; difference (%) –0.2 ± 17
	ST-segment depression at maximal exercise (mV): baseline 0.12 ± 0.06, 6 weeks 0.15 ± 0.11; difference (%) 41 ± 110
	Rate-pressure product at maximal exercise (mmHg × 100/min): baseline 130 ± 55, 6 weeks 131 ± 51; difference (%) 3 ± 20
	ST-segment depression at comparable workload (mV): baseline 0.10 ± 0.05, 6 weeks 0.13 ± 0.08; difference (%) 40 ± 77
	Rate-pressure product at comparable workload (mmHg × 100/min): baseline 123 ± 55, 6 weeks 126 ± 49; difference (%) 5 ± 23
Physical and functional abilities results exercise capacity: comparison	Treadmill test results – in the intervention group, compared with control, exercise duration was increased ($p = 0.03$), together with time to the onset of angina ($p = 0.01$) and a decrease of ST depression at comparable workload ($p = 0.01$) after 6 weeks of treatment
Health-related quality of life LASA details	Linear Analogue Self Assessment (LASA) scale for quality of life, a visual analogue scale 0–10 cm
	Two weeks before the first baseline tests and during the last 2 weeks of study, patients were instructed to record each day
Health-related quality of life results LASA: intervention group	LASA (cm): baseline 6.0 ± 0.8, 6 weeks 6.8 ± 1.0; difference (%) 15 ± 19 significant difference from baseline $p = 0.01$
Health-related quality of life results LASA: control group	LASA (cm): baseline 6.4 ± 1.7, 6 weeks 6.2 ± 1.1; difference (%) 1 ± 15
Health-related quality of life results LASA: comparison	Non-significant difference between groups
Complications and adverse effects outcomes SCS group	No complications
Adverse effects: control group	No complications

Appendix 6

Checklists for the published cost-effectiveness studies

Table 87 *Eddy, 1985[105]/Drummond and Jefferson, 1996[104] (BMJ) checklist for quality of studies*

A statement of the problem
A discussion of the need for modelling vs alternative methodologies
A description of the relevant factors and outcomes (disease-specific)
A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. Note: *n* = number of health states within submodel
A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence
A list of assumptions pertaining to: the structure of the model (eg. factors included, relationships, and distributions) and the data
A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis
The results derived from applying the model for the base case
The results of the sensitivity analyses; one-dimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold
A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect
A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity
A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results
A description of research in progress that could yield new data that could alter the results of the analysis

Table 88 *Eddy, 1985[105]/Drummond and Jefferson, 1996[104] (BMJ) checklist for modelling assessment*

A statement of the problem
A discussion of the need for modelling vs alternative methodologies
A description of the relevant factors and outcomes (disease-specific)
A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. Note: *n* = number of health states within submodel
A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence
A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships and distributions) and the data
A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis
The results derived from applying the model for the base case
The results of the sensitivity analyses; one-dimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold
A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect
A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity
A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results
A description of research in progress that could yield new data that could alter the results of the analysis

Appendix 7

Schematic models of decision tree and Markov model in the ABHI submission

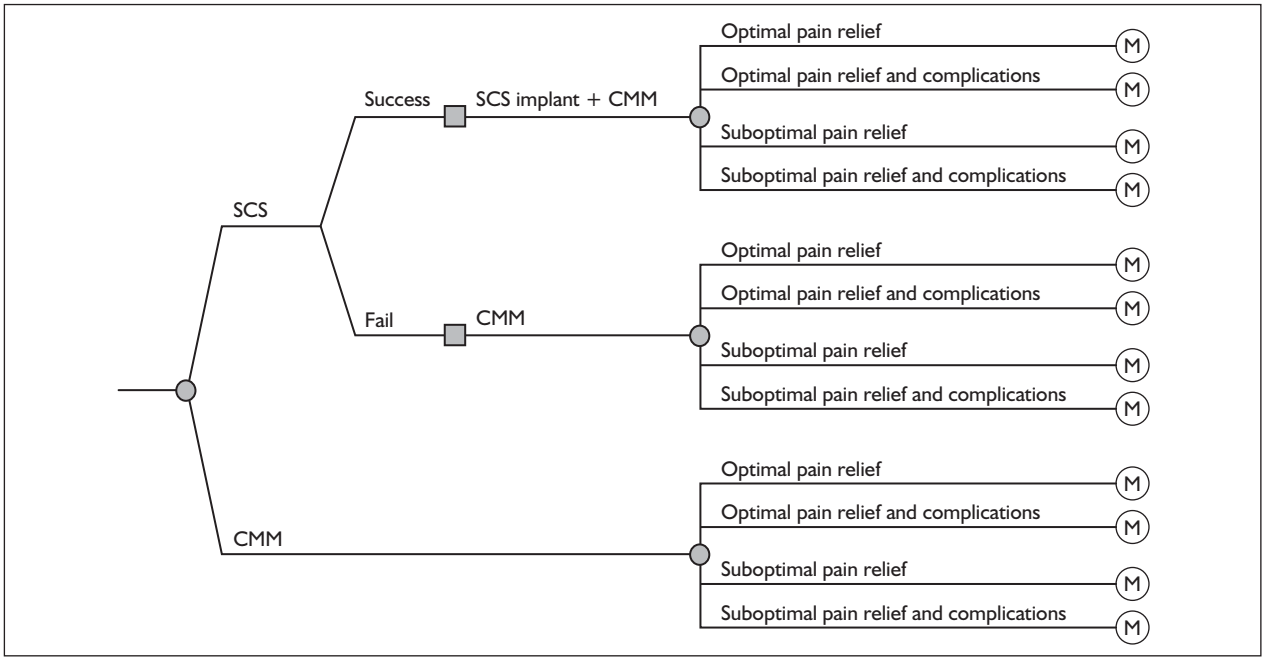

FIGURE 18 *Six-month decision tree for SCS+CMM versus CMM in FBSS and CRPS.*

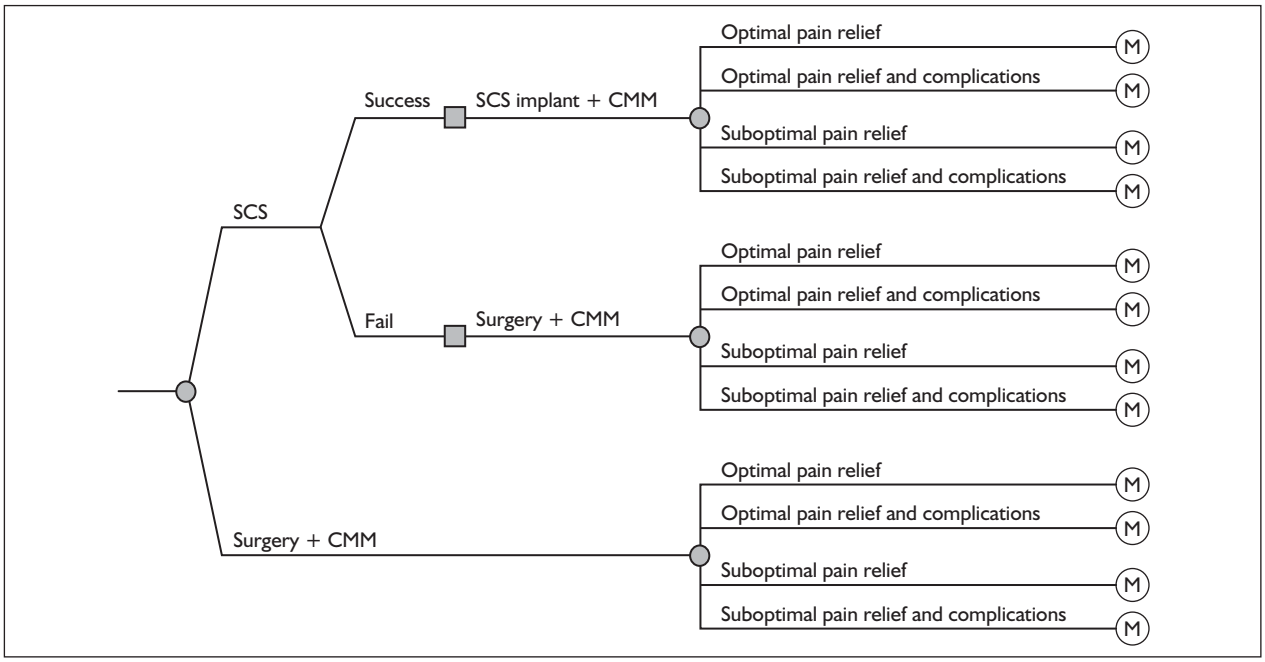

FIGURE 19 *Six-month decision tree for SCS+CMM versus reoperation in FBSS.*

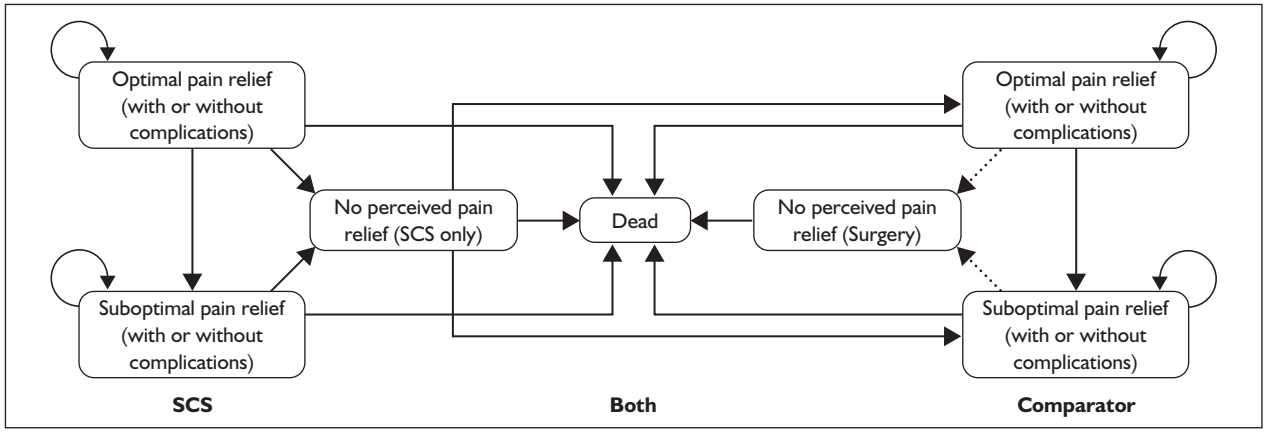

FIGURE 20 *Schematic of the long-term Markov model for FBSS.*

Appendix 8

Spinal cord stimulation devices price list

Table 89 *Implant: Medtronic Neurostimulation System price list*

Model number		
	Restore ADVANCED System	
37713	Implantable neurostimulator	£12,360
37742	External patient programmer	£541
	Total	£12,901
37702	Implantable neurostimulator	£8326
37742	External patient programmer	£541
	Total	£8867
	Synergy EZ System	
7427	Implantable neurostimulator	£7177
7435	External patient programmer	£568
	Total	£7745
	Synergy Veristrel System	
7427V	Implantable neurostimulator	£5145
7435	External patient programmer	£568
	Total	£5713
	Itrel 3 System	
7425	Implantable neurostimulator	£4995
7434	External patient programmer	£568
	Total	£5563
	Boston Scientific Company	
SC-1110	Implantable neurostimulator	£9424
	Remote Control	£586
	Kit-Charger	£627
	Total	£10,637

Appendix 9

Sensitivity analysis parameters

Table 90 *Sensitivity analysis parameters*

Variable description	Mean	Distribution	SE	Lower	Upper	Alpha	Beta	*n*	Source
Event probabilities									
FBSS: SCS + CMM vs CMM									
SCS trial success	0.8270	Beta	0.042194	0.7443	0.9097	43	9	52	Kumar *et al.*, 2007[59]
SCS % with complications	0.3170	Beta	0.016173	0.2853	0.3487	13	28	41	Kumar *et al.*, 2007[59]
SCS: 50% pt optimal pain relief	0.5854	Beta	0.029872	0.5268	0.6439	24	17	41	Kumar *et al.*, 2007[59]
CMM – no trial	1.0000								
CMM % with complications	0.0000	Constant	1	0	0				
CMM: 50% pt optimal pain relief	0.0930	Beta	0.004745	0.0837	0.1023	4	40	44	Kumar *et al.*, 2007[59]
FBSS: SCS + CMM vs reoperation									
SCS trial success – reoperation	0.7730	Beta	0.039439	0.6957	0.8503	17	6	23	North *et al.*, 2005[62]
SCS % with complications – reoperation	0.3170	Beta	0.016173	0.2853	0.3487	13	28	41	Kumar *et al.*, 2007[59]
SCS: 50% pt optimal pain relief – reoperation	1.0000	Constant	0.029872	0.5268	0.6439	17	0	17	North *et al.*, 2005[62]
Surgery: CMM % with complications	0.0000	Constant	1	0	0				
Surgery: CMM: 50% pt optimal pain relief	0.4620	Normal	0.004745	0.0837	0.1023				
CRPS: SCS + CMM vs CMM									
SCS trial success – CRPS	0.6667	Normal	0.034005	0.6	0.7333				
SCS % with complications – CRPS	0.3170	Beta	0.016173	0.2853	0.3487	13	28	41	Kumar *et al.*, 2007[59]
SCS: 50% pt optimal pain relief – CRPS	0.7500	Beta	0.038265	0.675	0.825	18	6	24	Kemler *et al.*, 2000[65]
CRPS:CMM % with complications	0.0000	Constant	1	0	0				Fritzell *et al.*, 2001[114]
CRPS:CMM: 50% pt optimal pain relief	0.4444	Beta	0.022679	0.4	0.4889	8	10	18	Assumption
CRPS:CMM: 50% pt optimal pain relief	0.4444	Uniform		0.088	0.4466				Assumption
Utilities									
FBSS: SCS + CMM vs CMM									
SCS vs CMM optimal pain relief 50% pt	0.598	Beta/Normal	0.030612	0.538	0.658	154	103	257	PROCESS

DOI: 10.3310/hta13170

Table 90 *Sensitivity analysis parameters (continued)*

Variable description	Mean	Distribution	SE	Lower	Upper	Alpha	Beta	*n*	Source
SCS vs CMM optimal pain relief and complications 50% pt	0.528	Beta/Normal	0.027041	0.475	0.581	181	162	342	PROCESS
SCS vs CMM suboptimal pain relief 50% pt	0.258	Beta/Normal	0.013265	0.232	0.284	285	819	1104	PROCESS
SCS vs CMM suboptimal pain relief and complications 50% pt	0.258	Beta/Normal	0.013265	0.232	0.284	285	819	1104	PROCESS
SCS vs CMM failure 50% pt	0.168	Beta/Normal	0.008673	0.151	0.185	319	1582	1901	PROCESS
FBSS: SCS + CMM vs reoperation									
SCS vs reoperation optimal pain relief 50% pt	0.598	Beta/Normal	0.030612	0.538	0.658	154	103	257	PROCESS
SCS vs reoperation optimal pain relief and complications 50% pt	0.528	Beta/Normal	0.027041	0.475	0.581	181	162	342	PROCESS
SCS vs reoperation suboptimal pain relief 50% pt	0.258	Beta/Normal	0.013265	0.232	0.284	285	819	1104	PROCESS
SCS vs reoperation suboptimal pain relief and complications 50% pt	0.258	Beta/Normal	0.013265	0.232	0.284	285	819	1104	PROCESS
SCS vs reoperation failure 50% pt	0.168	Beta/Normal	0.008673	0.151	0.185	319	1582	1901	PROCESS
CRPS: SCS + CMM vs CMM									
CRPS:SCS vs CMM optimal pain relief 50% pt	0.67	Beta				121	481	602	McDermott *et al.*, 2006[16]
CRPS:SCS vs CMM optimal pain relief and complications 50% pt	0.62	Beta							
CRPS:SCS vs CMM suboptimal pain relief 50% pt	0.46	Beta				305	297	602	McDermott *et al.*, 2006[16]
CRPS:SCS vs CMM suboptimal pain relief and complications 50% pt	0.41	Beta							
CRPS:SCS vs CMM failure 50% pt	0.16	Beta				138	464	602	McDermott *et al.*, 2006[16]
FBSS: SCS + CMM vs CMM									
SCS% with complications – optimal post Tx	0.3170	Beta	0.016173	0.2853	0.3487	13	28	41	Kumar *et al.*, 2007[59]
SCS% with complications – optimal cycle	0.1800	Beta	0.009184	0.162	0.198	315	1434	1749	
SCS% with complications – suboptimal post Tx	0.3170	Beta	0.016173	0.2853	0.3487	13	28	41	Kumar *et al.*, 2007[59]

continued

Table 90 *Sensitivity analysis parameters (continued)*

Variable description	Mean	Distribution	SE	Lower	Upper	Alpha	Beta	*n*	Source
SCS% with complications – suboptimal cycle	0.1800	Beta	0.009184	0.162	0.198	315	1434	1749	
CMM% with complications – optimal post Tx	0.0000	Constant							
CMM% with complications – optimal cycle	0.0000	Constant							
CMM% with complications – suboptimal post Tx	0.0000	Constant							
CMM% with complications – suboptimal cycle	0.0000	Constant							
Death rate per annum	0.0094	Constant							National Statistics[36]
SCS annual movement from optimal to suboptimal	0	Constant							
Annual probability of failing SCS	0.0324	Normal	0.042857	0	0.168				Kumar *et al.*, 2006[113]
CMM annual movement from optimal to suboptimal	0	Constant							
FBSS: SCS + CMM vs reoperation									
Reoperation annual % patients	0.0500	Beta	0.002551	0.045	0.055	365	6933	7298	Assumption
% patients optimal pain relief after reoperation	0.1900	Beta	0.009694	0.171	0.209	3	13	16	
Cost parameters									
Average cost of failed screening	£1041	Uniform		916	1166				Kumar *et al.*, 2006[117]
Average cost per trial stimulation	£4156	Normal	2646	3997	4315				Kumar *et al.*, 2006[117]
Average cost of implant	£10,066	Normal	5316	7854	13104				Kumar *et al.*, 2006[117]
Average cost of CMM (6 months), SCS + CMM	£1720	Uniform		1514	1926				Kumar *et al.*, 2007[59]
Average cost of CMM (6 months), CMM alone	£3468	Uniform		3025	3884				Kumar *et al.*, 2007[59]
Average cost of CMM (year 2 to 15)	£5704								Varies in terms of CMM cost reduction
Cost reduction of CMM alone after year 1	0.178	Triangular	0.013592	0.15096	0.20424				Kumar *et al.*, 2002[111]

Table 90 *Sensitivity analysis parameters (continued)*

Variable description	Mean	Distribution	SE	Lower	Upper	Alpha	Beta	*n*	Source
Cost of adverse events over 6 months	£388	Uniform		341	435				Kumar *et al.*, 2006[117]
Cost of adverse events subsequent cycles	£95								Assumption
Cost of reoperation	£4252	Normal	226.0204	3987	4873				NHS National Tariff R09[112]
Average cost of CMM (6 months), CRPS:SCS+CMM	£1691	Uniform		1514	1926				Kumar *et al.*, 2007[59]
Average cost of CMM (6 months), CRPS:CMM alone	£3468	Uniform		3052	3884				Kumar *et al.*, 2007[59]
Average cost of reimplant	£10,479	Normal	5316	7854	13,104				Kumar *et al.*, 2006[117]
Cost of adverse events over 6 months (reimplant)	£388	Uniform		341	435				Kumar *et al.*, 2006[117]
Device removal	£1041	Uniform		916	1166				Kumar *et al.*, 2006[117]

Appendix 10

Discounted costs and quality-adjusted life-years

Appendix 10.1: Results using different device longevity values

Table 91 *FBSS: SCS + CMM versus CMM alone*

Device longevity	Discounted ICER (£/QALY)	Discounted incremental cost (£)	Discounted incremental QALY	Undiscounted ICER (£/QALY)	Undiscounted incremental cost (£)	Undiscounted incremental QALY
1	£61,612	£76,252	1.24	£61,713	£80,920	1.31
2	£26,755	£33,414	1.25	£26,667	£35,287	1.32
3	£13,105	£16,425	1.25	£12,777	£16,968	1.33
4	£7996	£10,035	1.26	£7673	£10,203	1.33
5	£3574	£4491	1.26	£3155	£4201	1.33
6	£2913	£3661	1.26	£2591	£3451	1.33
7	£2304	£2896	1.26	£2065	£2750	1.33
8	−£1267	−£1594	1.26	−£1720	−£2293	1.33
9	−£1492	−£1878	1.26	−£1912	−£2549	1.33
10	−£1707	−£2147	1.26	−£2096	−£2794	1.33
11	−£1910	−£2403	1.26	−£2272	−£3029	1.33
12	−£2103	−£2647	1.26	−£2440	−£3254	1.33
13	−£2287	−£2878	1.26	−£2602	−£3470	1.33
14	−£2461	−£3098	1.26	−£2757	−£3676	1.33
15	−£5787	−£7289	1.26	−£6333	−£8453	1.33

Table 92 *FBSS: SCS + CMM versus reoperation*

Device longevity	Discounted ICER (£/QALY)	Discounted incremental cost (£)	Discounted incremental QALY	Undiscounted ICER (£/QALY)	Undiscounted incremental cost (£)	Undiscounted incremental QALY
1	£54,398	£71,323	1.31	£54,404	£75,724	1.39
2	£23,536	£31,283	1.33	£23,437	£33,071	1.41
3	£11,527	£15,403	1.34	£11,241	£15,949	1.42
4	£7043	£9430	1.34	£6771	£9625	1.42
5	£3167	£4248	1.34	£2819	£4015	1.42
6	£2588	£3472	1.34	£2326	£3314	1.42
7	£2055	£2757	1.34	£1866	£2659	1.42
8	−£1071	−£1440	1.34	−£1440	−£2055	1.43
9	−£1269	−£1705	1.34	−£1608	−£2294	1.43
10	−£1456	−£1957	1.34	−£1768	−£2523	1.43
11	−£1634	−£2196	1.34	−£1922	−£2743	1.43
12	−£1803	−£2424	1.34	−£2069	−£2953	1.43
13	−£1964	−£2640	1.34	−£2210	−£3155	1.43
14	−£2116	−£2845	1.34	−£2345	−£3348	1.43
15	−£5024	−£6763	1.35	−£5466	−£7813	1.43

Table 93 *CRPS: SCS + CMM versus CMM alone*

Device longevity	Discounted ICER (£/QALY)	Discounted incremental cost (£)	Discounted incremental QALY	Undiscounted ICER (£/QALY)	Undiscounted incremental cost (£)	Undiscounted incremental QALY
1	£186,923	£62,157	0.33	£187,274	£65,951	0.35
2	£80,388	£27,623	0.34	£80,124	£29,163	0.36
3	£40,017	£13,927	0.35	£39,042	£14,396	0.37
4	£25,095	£8775	0.35	£24,137	£8942	0.37
5	£12,264	£4306	0.35	£11,029	£4103	0.37
6	£10,351	£3637	0.35	£9398	£3498	0.37
7	£8591	£3020	0.35	£7877	£2933	0.37
8	−£1701	−£600	0.35	−£3030	−£1132	0.37
9	−£2349	−£829	0.35	−£3581	−£1338	0.37
10	−£2965	−£1046	0.35	−£4109	−£1536	0.37
11	−£3549	−£1252	0.35	−£4614	−£1725	0.37
12	−£4104	−£1449	0.35	−£5099	−£1907	0.37
13	−£4632	−£1635	0.35	−£5563	−£2081	0.37
14	−£5133	−£1812	0.35	−£6008	−£2247	0.37
15	−£14,658	−£5191	0.35	−£16,248	−£6098	0.38

Appendix 10.2: Results based on 4-year device longevity at 6 months and every subsequent year until 15 years

Table 94 *FBSS: SCS + CMM versus CMM (discounted)*

	Cost			QALY			
	SCS + CMM	CMM	Incremental costs	SCS + CMM	CMM	Incremental QALYs	ICER
6 months	£14,066	£3468	£10,598	0.2086	0.1442	0.0641	£165,247
Year 1	£16,243	£6991	£9252	0.418	0.288	0.130	£71,010
Year 2	£20,356	£12,727	£7630	0.828	0.572	0.256	£29,855
Year 3	£24,447	£18,357	£6090	1.226	0.854	0.372	£16,359
Year 4	£28,514	£23,885	£4628	1.614	1.133	0.481	£9624
Year 5	£39,539	£29,312	£10,227	1.991	1.411	0.58	£17,630
Year 6	£43,549	£34,639	£8910	2.36	1.686	0.674	£13,221
Year 7	£47,529	£39,869	£7660	2.719	1.958	0.761	£10,065
Year 8	£51,477	£45,003	£6473	3.07	2.228	0.842	£7690
Year 9	£61,086	£50,044	£11,042	3.411	2.495	0.915	£12,067
Year 10	£64,965	£54,992	£9973	3.745	2.76	0.984	£10,134
Year 11	£68,809	£59,850	£8959	4.071	3.023	1.048	£8549
Year 12	£72,615	£64,618	£7996	4.39	3.283	1.107	£7225
Year 13	£81,025	£69,300	£11,725	4.7	3.54	1.16	£10,110
Year 14	£84,754	£73,896	£10,858	5.005	3.795	1.209	£8977
Year 15	£88,443	£78,408	£10,035	5.303	4.048	1.255	£7996

Table 95 *FBSS: SCS + CMM versus CMM*

	Cost			QALY			
	SCS + CMM	CMM	Incremental costs	SCS + CMM	CMM	Incremental QALYs	ICER
6 months	£14,066	£3468	£10,598	0.2086	0.1442	0.0641	£165,247
Year 1	£16,262	£7022	£9240	0.420	0.289	0.131	£70,606
Year 2	£20,448	£12,858	£7590	0.837	0.578	0.258	£29,377
Year 3	£24,647	£18,638	£6009	1.246	0.868	0.378	£15,890
Year 4	£28,857	£24,362	£4495	1.648	1.157	0.491	£9162
Year 5	£40,374	£30,030	£10,344	2.041	1.447	0.594	£17,406
Year 6	£44,599	£35,644	£8956	2.429	1.736	0.693	£12,921
Year 7	£48,829	£41,202	£7627	2.812	2.026	0.786	£9707
Year 8	£53,062	£46,707	£6355	3.188	2.315	0.872	£7285
Year 9	£63,455	£52,159	£11,296	3.556	2.605	0.952	£11,872
Year 10	£67,687	£57,557	£10,130	3.921	2.894	1.027	£9865
Year 11	£71,917	£62,903	£9014	4.280	3.183	1.097	£8216
Year 12	£76,143	£68,198	£7945	4.634	3.471	1.162	£6835
Year 13	£85,562	£73,441	£12,121	4.981	3.760	1.222	£9921
Year 14	£89,774	£78,633	£11,141	5.325	4.048	1.278	£8718
Year 15	£93,979	£83,775	£10,203	5.665	4.335	1.330	£7673

Table 96 *FBSS: SCS + CMM versus reoperation (discounted)*

	Cost			QALY			
	SCS + CMM	CMM	Incremental costs	SCS + CMM	CMM	Incremental QALYs	ICER
6 months	£13,620	£4252	£9368	0.269	0.208	0.062	£150,803
Year 1	£15,875	£7735	£8140	0.542	0.413	0.129	£63,201
Year 2	£20,076	£13,394	£6682	1.074	0.818	0.256	£26,114
Year 3	£24,247	£18,949	£5297	1.594	1.218	0.375	£14,113
Year 4	£28,387	£24,404	£3982	2.100	1.613	0.488	£8167
Year 5	£39,024	£29,760	£9264	2.592	2.001	0.590	£15,698
Year 6	£43,096	£35,018	£8078	3.074	2.385	0.689	£11,722
Year 7	£47,133	£40,180	£6952	3.545	2.763	0.782	£8890
Year 8	£51,132	£45,249	£5883	4.005	3.135	0.869	£6768
Year 9	£60,417	£50,226	£10,191	4.451	3.503	0.949	£10,743
Year 10	£64,340	£55,112	£9227	4.890	3.865	1.025	£9000
Year 11	£68,222	£59,910	£8312	5.319	4.222	1.097	£7577
Year 12	£72,063	£64,620	£7443	5.738	4.574	1.164	£6393
Year 13	£80,202	£69,245	£10,957	6.145	4.920	1.225	£8943
Year 14	£83,959	£73,786	£10,174	6.546	5.262	1.284	£7924
Year 15	£87,674	£78,244	£9430	6.938	5.599	1.339	£7043

Table 97 *FBSS: SCS + CMM versus reoperation*

	Cost			QALY			
	SCS + CMM	CMM	Incremental costs	SCS + CMM	CMM	Incremental QALYs	ICER
6 months	£13,620	£4252	£9368	0.269	0.208	0.062	£150,803
Year 1	£15,895	£7766	£8130	0.544	0.415	0.129	£62,833
Year 2	£20,169	£13,524	£6646	1.086	0.827	0.259	£25,689
Year 3	£24,451	£19,226	£5224	1.619	1.238	0.381	£13,701
Year 4	£28,737	£24,875	£3863	2.144	1.646	0.498	£7763
Year 5	£39,848	£30,468	£9380	2.657	2.052	0.605	£15,512
Year 6	£44,139	£36,009	£8130	3.165	2.456	0.709	£11,467
Year 7	£48,430	£41,496	£6933	3.666	2.858	0.808	£8583
Year 8	£52,718	£46,931	£5787	4.159	3.257	0.901	£6421
Year 9	£62,760	£52,313	£10,447	4.642	3.655	0.987	£10,583
Year 10	£67,039	£57,644	£9395	5.120	4.050	1.071	£8775
Year 11	£71,312	£62,924	£8388	5.592	4.443	1.150	£7295
Year 12	£75,577	£68,154	£7423	6.057	4.833	1.224	£6063
Year 13	£84,692	£73,333	£11,358	6.514	5.221	1.293	£8788
Year 14	£88,936	£78,463	£10,473	6.966	5.607	1.359	£7707
Year 15	£93,169	£83,544	£9625	7.413	5.991	1.422	£6771

Table 98 *CRPS: SCS + CMM versus CMM (discounted)*

	Cost			QALY			
	SCS + CMM	CMM	Incremental costs	SCS + CMM	CMM	Incremental QALYs	ICER
6 months	£12,214	£3468	£8746	0.293	0.277	0.016	£542,898
Year 1	£14,639	£6953	£7686	0.585	0.550	0.035	£219,597
Year 2	£19,041	£12,615	£6425	1.160	1.089	0.071	£90,842
Year 3	£23,403	£18,174	£5229	1.724	1.620	0.104	£50,288
Year 4	£27,725	£23,633	£4093	2.277	2.142	0.135	£30,343
Year 5	£37,638	£28,992	£8646	2.818	2.656	0.162	£53,447
Year 6	£41,874	£34,253	£7622	3.350	3.161	0.188	£40,458
Year 7	£46,067	£39,419	£6649	3.872	3.659	0.213	£31,209
Year 8	£50,216	£44,491	£5725	4.384	4.148	0.236	£24,273
Year 9	£58,909	£49,470	£9439	4.885	4.629	0.255	£36,950
Year 10	£62,966	£54,360	£8606	5.378	5.103	0.275	£31,307
Year 11	£66,975	£59,160	£7815	5.862	5.569	0.293	£26,691
Year 12	£70,938	£63,873	£7065	6.337	6.027	0.309	£22,842
Year 13	£78,595	£68,501	£10,094	6.801	6.478	0.323	£31,234
Year 14	£82,462	£73,044	£9417	7.259	6.922	0.337	£27,943
Year 15	£86,280	£77,505	£8775	7.708	7.358	0.350	£25,095

Table 99 *CRPS: SCS+CMM versus CMM*

	Cost			QALY			
	SCS + CMM	CMM	Incremental costs	SCS + CMM	CMM	Incremental QALYs	ICER
6 months	£12,214	£3468	£8746	0.293	0.277	0.016	£542,898
Year 1	£14,660	£6984	£7676	0.588	0.553	0.035	£218,301
Year 2	£19,139	£12,745	£6394	1.173	1.101	0.072	£89,395
Year 3	£23,618	£18,452	£5166	1.752	1.646	0.106	£48,894
Year 4	£28,093	£24,103	£3989	2.324	2.187	0.138	£28,981
Year 5	£38,446	£29,701	£8745	2.889	2.723	0.166	£55,767
Year 6	£42,911	£35,245	£7666	3.450	3.256	0.194	£39,560
Year 7	£47,367	£40,735	£6632	4.004	3.784	0.220	£30,147
Year 8	£51,815	£46,173	£5641	4.553	4.309	0.244	£23,079
Year 9	£61,218	£51,559	£9658	5.095	4.830	0.266	£36,359
Year 10	£65,643	£56,893	£8750	5.633	5.346	0.287	£30,502
Year 11	£70,056	£62,177	£7879	6.166	5.829	0.307	£25,702
Year 12	£74,455	£67,409	£7046	6.693	6.368	0.325	£21,690
Year 13	£83,031	£72,592	£10,439	7.213	6.873	0.340	£30,664
Year 14	£87,399	£77,724	£9674	7.730	7.374	0.356	£27,170
Year 15	£91,750	£82,808	£8942	8.242	7.872	0.370	£24,137

Appendix 10.3: Results using different device cost values

Table 100 *FBSS: SCS + CMM versus CMM alone*

Device cost	Discounted ICER (£/ QALY)	Discounted incremental cost (£)	Discounted incremental QALY	Undiscounted ICER (£/ QALY)	Undiscounted incremental cost (£)	Undiscounted incremental QALY
£5000	£2563	£3216	1.26	£2282	£3035	1.33
£6000	£4542	£5700	1.26	£4246	£5646	1.33
£7000	£6521	£8184	1.26	£6210	£8258	1.33
£8000	£8500	£10,668	1.26	£8173	£10,869	1.33
£9000	£10,480	£13,153	1.26	£10,137	£13,481	1.33
£10,000	£12,459	£15,637	1.26	£12,101	£16,092	1.33
£11,000	£14,438	£18,121	1.26	£14,065	£18,704	1.33
£12,000	£16,418	£20,605	1.26	£16,029	£21,316	1.33
£13,000	£18,397	£23,089	1.26	£17,992	£23,927	1.33
£14,000	£20,376	£25,573	1.26	£19,956	£26,539	1.33
£15,000	£22,356	£28,057	1.26	£21,920	£29,150	1.33

Table 101 *FBSS: SCS + CMM versus reoperation*

Device cost	Discounted ICER (£/ QALY)	Discounted incremental cost (£)	Discounted incremental QALY	Undiscounted ICER (£/ QALY)	Undiscounted incremental cost (£)	Undiscounted incremental QALY
£5000	£2283	£3056	1.34	£2057	£2925	1.42
£6000	£4017	£5378	1.34	£3775	£5366	1.42
£7000	£5751	£7700	1.34	£5492	£7807	1.42
£8000	£7485	£10,022	1.34	£7209	£10,248	1.42
£9000	£9219	£12,344	1.34	£8926	£12,689	1.42
£10,000	£10,953	£14,666	1.34	£10,643	£15,130	1.42
£11,000	£12,687	£16,988	1.34	£12,360	£17,571	1.42
£12,000	£14,421	£19,310	1.34	£14,077	£20,012	1.42
£13,000	£16,156	£21,632	1.34	£15,794	£22,453	1.42
£14,000	£17,890	£23,953	1.34	£17,511	£24,894	1.42
£15,000	£19,624	£26,275	1.34	£19,228	£27,335	1.42

Table 102 *CRPS: SCS + CMM versus CMM alone*

Device cost	Discounted ICER (£/QALY)	Discounted incremental cost (£)	Discounted incremental QALY	Undiscounted ICER (£/QALY)	Undiscounted incremental cost (£)	Undiscounted incremental QALY
£5000	£9374	£3278	0.35	£8537	£3163	0.37
£6000	£15,101	£5280	0.35	£14,220	£5268	0.37
£7000	£20,828	£7283	0.35	£19,903	£7374	0.37
£8000	£26,555	£9286	0.35	£25,586	£9479	0.37
£9000	£32,282	£11,288	0.35	£31,269	£11,584	0.37
£10,000	£38,010	£13,291	0.35	£36,952	£13,690	0.37
£11,000	£43,737	£15,293	0.35	£42,635	£15,795	0.37
£12,000	£49,464	£17,296	0.35	£48,317	£17,900	0.37
£13,000	£55,191	£19,299	0.35	£54,000	£20,006	0.37
£14,000	£60,918	£21,301	0.35	£59,683	£22,111	0.37
£15,000	£66,646	£23,304	0.35	£65,366	£24,216	0.37

Appendix 10.4: Impact of device average price and device longevity on incremental cost-effectiveness ratio

Table 103 *FBSS: SCS + CMM versus reoperation – discounted ICERs (£/QALY)*

Longevity (years)	Device cost										
	£5000	**£6000**	**£7000**	**£8000**	**£9000**	**£10,000**	**£11,000**	**£12,000**	**£13,000**	**£14,000**	**£15,000**
1	£37,142	£43,429	£49,715	£56,001	£62,288	£68,574	£74,861	£81,147	£87,434	£93,720	£100,006
2	£14,424	£17,744	£21,063	£24,383	£27,703	£31,022	£34,342	£37,662	£40,981	£44,301	£47,621
3	£5583	£7749	£9914	£12,079	£14,244	£16,409	£18,575	£20,740	£22,905	£25,070	£27,235
4	£2283	£4017	£5751	£7485	£9219	£10,953	£12,687	£14,421	£16,156	£17,890	£19,624
5	–£570	£791	£2153	£3514	£4876	£6238	£7599	£8961	£10,322	£11,684	£13,046
6	–£997	£309	£1615	£2921	£4227	£5533	£6839	£8145	£9451	£10,757	£12,063
7	–£1389	–£135	£1120	£2374	£3629	£4884	£6138	£7393	£8648	£9902	£11,157
8	–£3690	–£2736	–£1782	–£828	£126	£1080	£2034	£2988	£3943	£4897	£5851
9	–£3836	–£2900	–£1965	–£1030	–£95	£840	£1775	£2711	£3646	£4581	£5516
10	–£3974	–£3056	–£2139	–£1222	–£305	£612	£1529	£2447	£3364	£4281	£5198
11	–£4105	–£3204	–£2304	–£1404	–£504	£396	£1296	£2196	£3096	£3996	£4896
12	–£4229	–£3345	–£2461	–£1578	–£694	£190	£1074	£1958	£2841	£3725	£4609
13	–£4347	–£3479	–£2611	–£1742	–£874	–£5	£863	£1731	£2600	£3468	£4336
14	–£4460	–£3606	–£2752	–£1899	–£1045	–£191	£663	£1516	£2370	£3224	£4077

Table 104 *CRPS: SCS + CMM versus CMM alone – discounted ICERs (£/QALY)*

Longevity (years)	Device cost										
	£5000	**£6000**	**£7000**	**£8000**	**£9000**	**£10,000**	**£11,000**	**£12,000**	**£13,000**	**£14,000**	**£15,000**
1	£128,240	£149,618	£170,996	£192,375	£213,753	£235,131	£256,509	£277,888	£299,266	£320,644	£342,022
2	£49,988	£61,063	£72,137	£83,212	£94,287	£105,362	£116,437	£127,512	£138,586	£149,661	£160,736
3	£20,335	£27,505	£34,675	£41,846	£49,016	£56,187	£63,357	£70,528	£77,698	£84,868	£92,039
4	£9374	£15,101	£20,828	£26,555	£32,282	£38,010	£43,737	£49,464	£55,191	£60,918	£66,646
5	–£51	£4435	£8921	£13,408	£17,894	£22,380	£26,866	£31,352	£35,839	£40,325	£44,811
6	–£1456	£2845	£7147	£11,448	£15,749	£20,050	£24,352	£28,653	£32,954	£37,256	£41,557
7	–£2749	£1382	£5513	£9644	£13,775	£17,906	£22,037	£26,168	£30,299	£34,430	£38,561
8	–£10,309	–£7173	–£4037	–£902	£2234	£5370	£8505	£11,641	£14,776	£17,912	£21,048
9	–£10,784	–£7711	–£4639	–£1566	£1507	£4580	£7653	£10,726	£13,799	£16,872	£19,945
10	–£11,236	–£8223	–£5210	–£2196	£817	£3831	£6844	£9858	£12,871	£15,884	£18,898
11	–£11,666	–£8709	–£5752	–£2795	£162	£3119	£6076	£9033	£11,989	£14,946	£17,903
12	–£12,074	–£9170	–£6267	–£3364	–£461	£2442	£5346	£8249	£11,152	£14,055	£16,958
13	–£12,461	–£9609	–£6757	–£3904	–£1052	£1800	£4652	£7504	£10,357	£13,209	£16,061
14	–£12,829	–£10,025	–£7221	–£4418	–£1614	£1190	£3994	£6797	£9601	£12,405	£15,209

Table 105 *CRPS: SCS + CMM versus CMM alone – undiscounted ICERs (£/QALY)*

Longevity (years)	Device cost										
	£5000	£6000	£7000	£8000	£9000	£10,000	£11,000	£12,000	£13,000	£14,000	£15,000
1	£128,358	£149,821	£171,284	£192,747	£214,210	£235,673	£257,136	£278,599	£300,062	£321,525	£342,989
2	£49,658	£60,757	£71,855	£82,954	£94,052	£105,151	£116,249	£127,347	£138,446	£149,544	£160,643
3	£19,485	£26,609	£33,734	£40,859	£47,983	£55,108	£62,233	£69,357	£76,482	£83,607	£90,731
4	£8537	£14,220	£19,903	£25,586	£31,269	£36,952	£42,635	£48,317	£54,000	£59,683	£65,366
5	–£1090	£3325	£7740	£12,155	£16,569	£20,984	£25,399	£29,814	£34,229	£38,644	£43,059
6	–£2288	£1969	£6227	£10,484	£14,741	£18,998	£23,256	£27,513	£31,770	£36,027	£40,284
7	–£3405	£705	£4815	£8,25	£13,035	£17,145	£21,255	£25,365	£29,475	£33,585	£37,695
8	–£11,416	–£8361	–£5306	–£2251	£804	£3859	£6914	£9969	£13,024	£16,079	£19,134
9	–£11,821	–£8819	–£5817	–£2815	£186	£3188	£6190	£9192	£12,193	£15,195	£18,197
10	–£12,208	–£9258	–£6307	–£3356	–£405	£2545	£5496	£8447	£11,397	£14,348	£17,299
11	–£12,580	–£9678	–£6776	–£3874	–£972	£1929	£4831	£7733	£10,635	£13,537	£16,438
12	–£12,936	–£10,081	–£7226	–£4371	–£1516	£1339	£4194	£7049	£9904	£12,759	£15,614
13	–£13,277	–£10,466	–£7656	–£4846	–£2036	£774	£3584	£6394	£9204	£12,014	£14,824
14	–£13,603	–£10,836	–£8069	–£5302	–£2535	£232	£2999	£5766	£8533	£11,300	£14,067

Appendix 11

Probabilistic sensitivity analyses

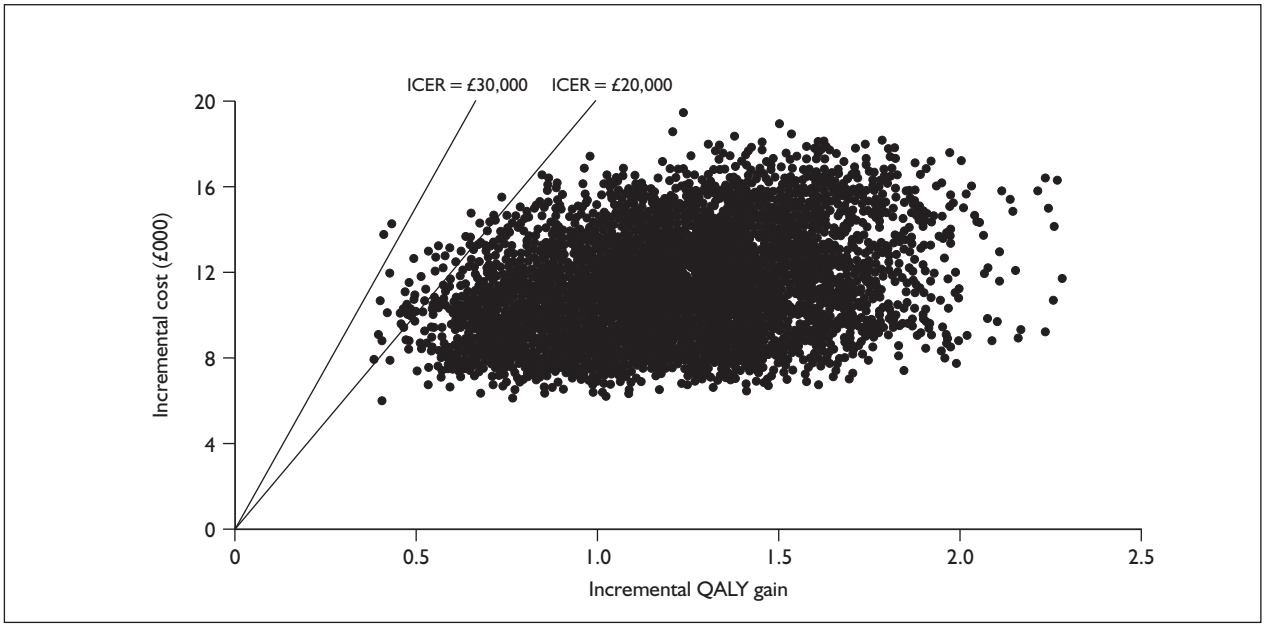

FIGURE 21 *Scatter plot of base-case results for FBSS: SCS + CMM versus CMM alone.*

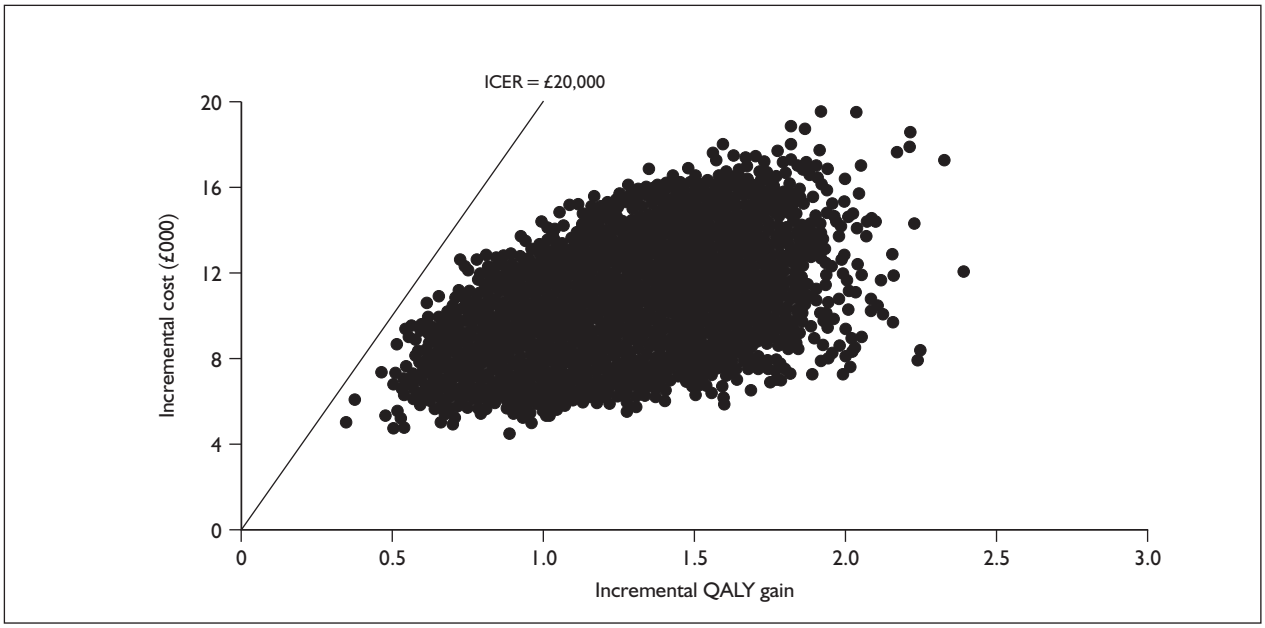

FIGURE 22 *Scatter plot of base-case results for FBSS: SCS + CMM versus reoperation.*

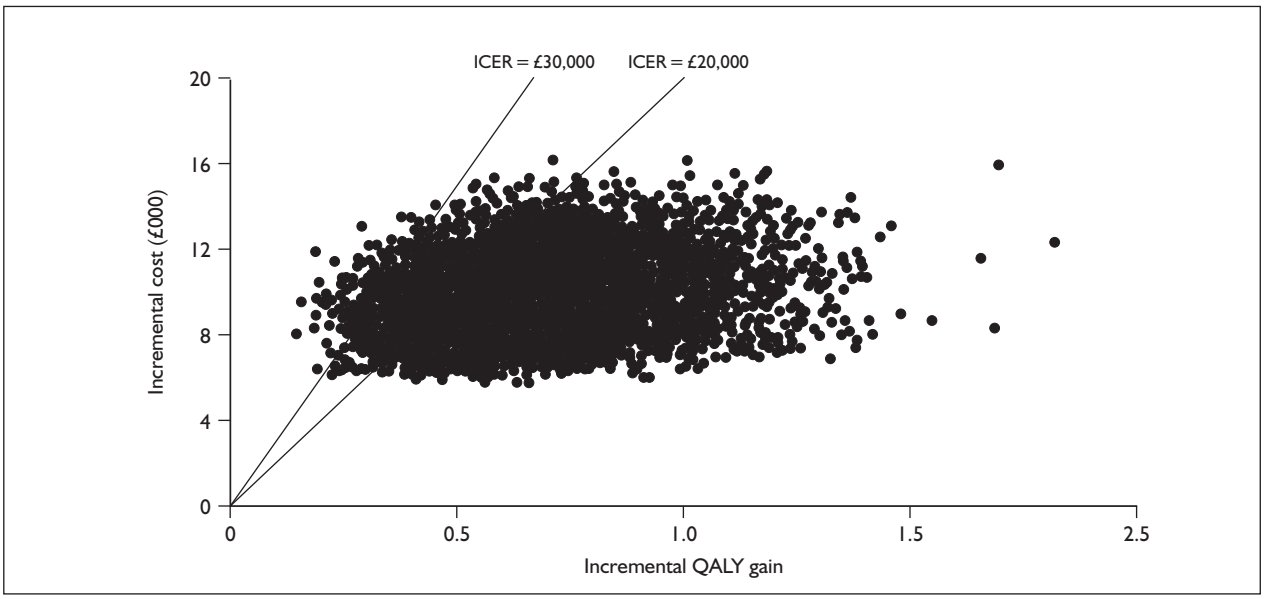

FIGURE 23 *Scatter plot of base-case results for CRPS: SCS + CMM versus CMM.*

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We look forward to hearing from you.

The NIHR Coordinating Centre for Health Technology Assessment
Alpha House, Enterprise Road
Southampton Science Park
Chilworth
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278