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Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin

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About ScHARR

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The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence. ScHARR-TAG is part of a wider collaboration of six units from other regions. The other units are: Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

Contributions of authors

E.L. Simpson conducted the clinical effectiveness review, A. Duenas conducted the cost effectiveness review, D. Papaioannou conducted the literature searches, all authors were involved in preparing the protocol for the report.

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1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

DEFINITION OF TERMS

Angina pectoris	Ischaemic chest pain (usually due to 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
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
MQS	Medication quantification scale
NHP	Nottingham Health Profile
NSUKI	Neuromodulation Society of UK and Ireland
PMR	Percutaneous myocardial revascularisation
PT	Physical therapy
QALY	Quality adjusted life years
RCT	Randomised controlled trial
RD	Risk difference
RR	Relative risk
SCS	Spinal cord stimulation
SF36	Short Form 36
SIP	Sickness Impact Profile
TcpO2	Transcutaneous oxygen pressure
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue scale

2. EXECUTIVE SUMMARY

2.1 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.

2.2 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?"

2.3 Methods

A systematic review of the literature sought clinical and cost effectiveness data for SCS in adults with chronic neuropathic or ischaemic pain who had had an inadequate response to medical or surgical treatment other than SCS. Comparators were medical or surgical treatment appropriate to condition. Clinical outcomes sought included pain, health-related quality of life (HRQoL) and adverse effects.

Economic analyses were performed to model the cost effectiveness and cost utility of spinal cord stimulation 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 six 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. RCT data 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 re-operation. 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 National Health Service 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 due to 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.

2.4 Results

Eleven randomised controlled trials were included in the clinical effectiveness review, three of neuropathic pain, and eight ischaemic pain. Comparators were relevant to UK practice. Good quality, adequately powered trials were available for neuropathic conditions FBSS and CRPS type I, and suggested SCS was more effective than CMM in reducing pain. The main limitation of the ischaemic pain trials was small sample sizes, meaning 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 angina pain onset during exercise at short-term follow-up, though not more so than coronary artery bypass grafting 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 £[redacted], suggested that the cost effectiveness estimates for SCS in patients with FBSS who had inadequate response 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 device longevity was greater than 3 years the results showed that the cost effectiveness estimates for SCS for FBSS (compared to CMM or re-operation) were below £20,000 per QALY gained. In CRPS (compared to CMM) when using a device longevity of 3 years the ICER was £40,017 per QALY gained.

When the SCS device costs varied in a range from £5,000 to £15,000, the ICERs ranged from £2,563 per QALY to £22,356 per QALY for FBSS when compared to CMM and from £2,283 per QALY to £19,624 per QALY for FBSS compared to re-operation. For CRPS the ICERs ranged from £9,374 per QALY to £66,646 per QALY. In CRPS, the maximum average price for a device to remain under an estimated ICER of £20,000 per QALY was £6,000 and £8,000 to remain under £30,000 per QALY.

If device longevity (1 to 14 years) and device average price (£5,000 to £15,000) were varied simultaneously, ICERs were below or very close to £30,000 per QALY when device longevity was 3 years. ICERs were 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 (cost less and accrued more survival benefits) over CABG.

2.5 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.

2.6 Conclusions

Evidence suggested SCS was effective in reducing 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 angina short-term.

3. BACKGROUND

3.1. 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 three 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 pathophysiologic phenomenon. 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 failed back surgery syndrome 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 has 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); and oedema (accumulation of tissue fluid), changes in skin blood flow, or abnormal sudomotor activity (nerves that stimulate sweat glands) in region of pain; and 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; and oedema,

changes in skin blood flow, or abnormal sudomotor activity in region of pain; and 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 two 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 alternatively be due to Syndrome X, in which the coronary vessels appear normal.

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] 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 size and to 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 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 40 to 69, and found the prevalence to be 0.24%, with some increase with increasing age.[13] A UK study of men aged 40 to 59 found a prevalence of definite angina of 4.8%, and 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. A European survey of chronic pain (including but not limited to neuropathic pain) in 15 European countries and Israel showed that 19% of adults suffer chronic pain of moderate to severe intensity.[15] In interviews with 4,839 patients, it was found that chronic pain had a severe impact in the following daily activities: sleeping, exercising lifting, household chores, walking, attending social activities, working outside home, maintaining and 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 whilst 34% of the respondents were less able to attend social activities, and 65 % were less able or unable to sleep.

Breivik *et al.* reported that from 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% lost their job, 16% changed jobs responsibilities, and 18% changed jobs entirely. The ability to work on people that suffer chronic pain can have a direct impact on the society 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.[15]

In a cross-sectional survey (observational), McDermott *et al.* reported the association of neuropathic pain severity with EQ-5D.[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 EQ-5D scores. Scores of 0-3, 4-6 and 7-10 represented mild, moderate and severe pain ratings, respectively. The EQ-5D scores were 0.67 for mild, 0.46 for moderate and 0.16 for severe. 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 critical limb ischaemia (CLI) which includes diagnosis using 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 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 30% reduction on a rating scale from 0 to 10.[23,21]

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 health-related quality of life (HRQoL). Generic measures (that is, designed to measure any health-related changes in quality of life) include the Nottingham Health Profile (NHP), EuroQol 5D (EQ5D), the Sickness Impact Profile (SIP) and the Short Form 36 (SF-36). The NHP has 2 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 26,27,28]

EQ5D has 15 questions assessing five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[29] The Sickness Impact Profile 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 Short Form 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]

3.2. 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 condition such as non-steroidal anti-inflammatory drugs (NSAIDs) 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 (TENS). Antidepressants are provided, as depression is often comordid 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 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, preferred treatment is revascularisation (for angina this includes coronary artery bypass grafting (CABG) and percutaneous myocardial revascularisation (PMR), for CLI percutaneous angioplasty or distal grafting), however not all patients with chronic ischaemic pain are eligible for this. For

chronic critical limb ischaemia, amputation is often considered. Non-surgical treatments for CLI are prolonged bedrest and analgesia.

Current service cost

In a European survey, Breivik *et al.* 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 5,800 per 100,000 population. Therefore, an approximate of 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 estimated of approximately 4,051 patients a year would be suitable for SCS treatment if just 1% of the estimated chronic pain population are 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 that suffer from angina will develop refractory angina.[39] This represents an estimated cost of refractory angina in the UK of approximately £11-£22 million.

In the year 2000 the estimated cost of critical limb ischaemia 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 spinal cord stimulation (SCS) in FBSS and CRPS type I. [21] They also suggest the need for comparative trials in other indications, though reporting positive findings from case series for SCS in CRPS type II, peripheral nerve injury, diabetic neuropathy, post-herpetic neuralgia, amputation pain, partial spinal cord injury.[21]

Detailed guidelines produced by the British Pain Society 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 (RCA), Royal College of General Practitioners and BPS, [43,35,44] Quality Improvement Scotland,[45] and IASP.[46] Guidelines support a multi-disciplinary approach to pain management.

3.3. Description of technology under assessment

Spinal cord stimulation (SCS) 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. A 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]

SCS (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 multi-disciplinary care team. Expected benefits of SCS are reduction in pain, improved quality of life, and may reduce 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. SCS is not effective for nociceptive pain.[35] SCS has the advantage of being reversible.

The British Pain Society suggests that SCS may be considered when first line therapies for chronic pain have failed. A typical SCS device has four components: (1) 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, (2) implanted leads with a variable number of electrode contacts near the spinal cord, (3) an extension cable that connects the electrode(s) to the pulse generator, and (4) 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, along with an implantable generator and controller that allows 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 by means of an implantable pulse generator (IPG). An alternative form of pulse generation is the radio-frequency (RF) receiver. The choice of SCS device depends on individual patient needs (e.g. pain patterns, power and coverage needs) and preference as well as the physician's preference. A number of SCS devices from the following manufacturers have received European approval to market (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 British Pain Society 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.[48,49,50,51,21 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 Neuromodulation Society of UK and Ireland (NSUKI)[55] suggests that HES 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. EFNS suggest that test stimulation is not a guarantee of long-term success, but can identify patients who don't like the sensation or can't 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 is 645.[54] Assuming an associated cost for 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 year 2011. This estimation is calculated considering the device costs, screening, implantation costs, adverse events and healthcare resources used over the patients management.

It is uncertain at the moment what proportion of the individuals who are eligible to SCS treatment will receive it in the future. If SCS is recommend for the treatment of neuropathic

and ischaemic pain then more funding in the provision of chronic pain services in England and Wales may be required.

4. DEFINITION OF THE DECISION PROBLEM

4.1 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 spinal cord stimulation. Spinal cord stimulator devices comprised spinal cord stimulators with implantable pulse generator systems (non-rechargeable and rechargeable) and spinal cord stimulators with radio-frequency receiver systems. This intervention was compared with medical and/or surgical treatment (appropriate to condition) that does 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 spinal cord stimulation, or were considered unsuitable for alternative surgical therapy. This review excluded chronic pain which 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).

4.2 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 NHS in England and Wales.

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

5.1.1 Identification of studies

A comprehensive search was undertaken to systematically identify clinical effectiveness literature concerning spinal cord stimulation 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, Embase, CINAHL, BIOSIS, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Controlled Trials Register (CCTR), the Science Citation Index and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA) and OHE HEED. Pre-Medline was also searched to identify any studies not yet indexed on Medline. Current research was identified through searching the National Research Register (NRR), the Current Controlled Trials register and the MRC Clinical Trials Register. Sources such as Google Scholar were searched. The table 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 (IASP), the European Taskforce guidelines for neurostimulation therapy for neuropathic pain on the European Federation for Neurological Societies (EFNS) website. Any industry submissions, as well as relevant systematic reviews were hand-searched in order 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 removed.

5.1.2 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 radio-frequency 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 spinal cord stimulation.

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 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 as 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 some of which 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, and they are prone to selection bias, and as with other non-randomised studies would expect bias toward positive results.[57]

Exclusion criteria

Trials were excluded if the intervention was neurostimulation that involves stimulation of other parts of the nervous system (e.g. peripheral nerves, deep brain), patients with prior use of SCS, pregnancy, 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.

5.1.3 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 5. 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 6). Pre-specified outcomes were tabulated and discussed within a descriptive synthesis.

5.2 Results

5.2.1 Quantity and quality of research available

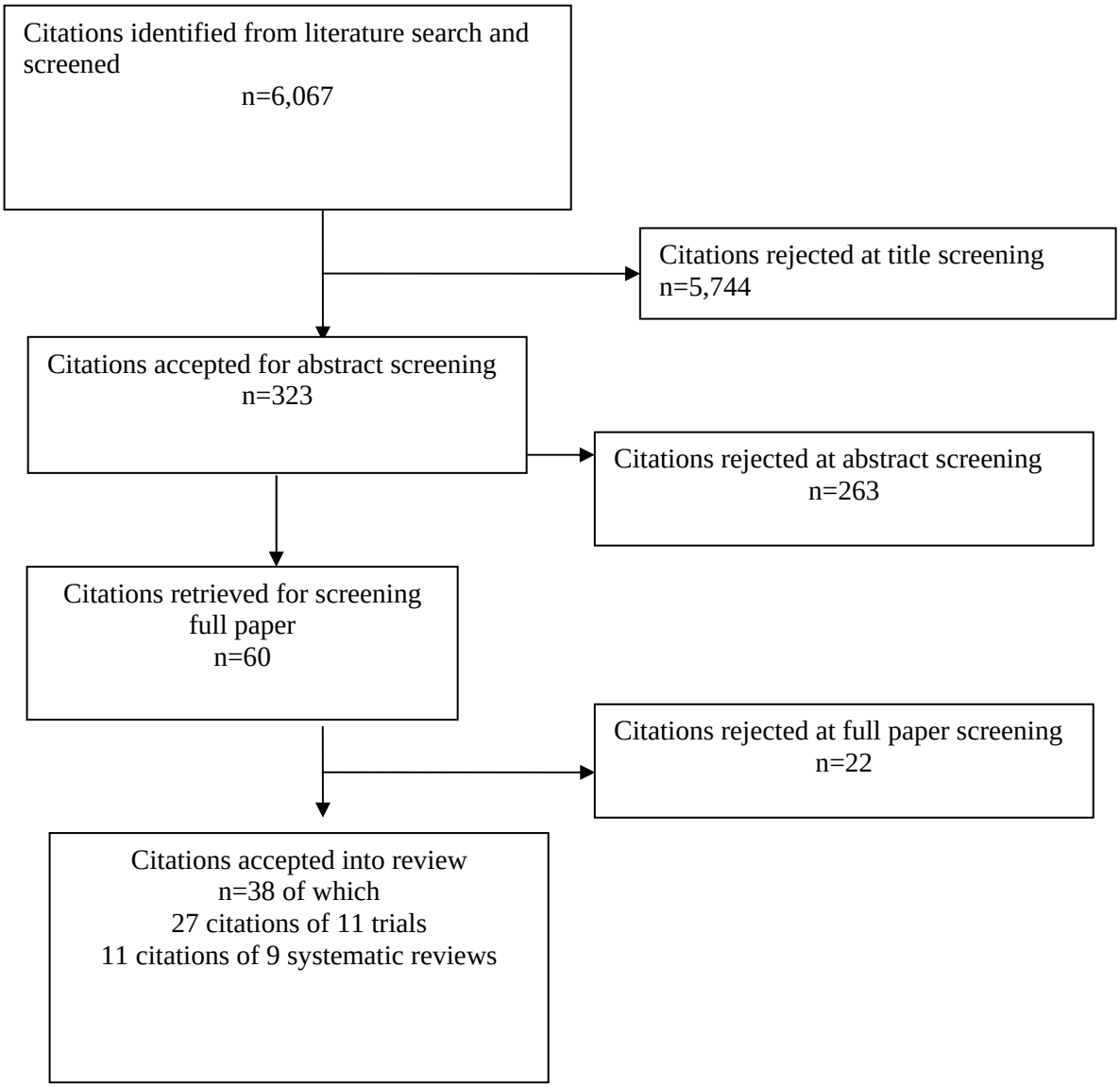
The search for clinical effectiveness literature yielded 6,067 article citations when duplicates had been removed. Figure 1 shows study selection. Citations presenting purely economic analyses were not included in this chapter. References excluded at the full paper screening stage, with reason for exclusion, are presented in Appendix 4.

There were twenty-seven references of eleven trials accepted into the review (including publication of pilot study of one of the included trials[58]). These comprised three

trials[59,60,61,62,63,64,65,66,67] of neuropathic pain and eight trials[68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84] of ischaemic pain.

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

Figure 1: Flow diagram of study selection



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 6.

Table 1 Summary of neuropathic pain trials

Trial	Indication	Intervention	Comparator	Total number randomised	Data at follow-up	Primary outcome
PROCESS [59,60,61]	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 [62,63,64]	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 [65,66,67]	Complex regional pain syndrome type I	SCS plus physical therapy	Physical therapy	54	6, 24 and 60 months	Visual analogue scale (VAS) 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 [68,69,70,71,72] (pilot study[58])	Critical limb ischaemia	SCS plus CMM	CMM	120	6, 12, 18 and 24 months	Limb salvage rates; pain relief
Suy[73]	Critical limb ischaemia	SCS plus CMM	CMM	38	24 months	Limb salvage rates
Jivegard[74]	Critical limb ischaemia	SCS plus peroral analgesics	Peroral analgesics	51	18 months	Limb salvage rates
Claeys[75,76,77,78]	Critical limb ischaemia	SCS plus Prostaglandin E1	Prostaglandin E1 (PGE1)	86	12 months	Limb salvage rates
DeJongste [79]	Angina pectoris	SCS	No SCS	17	6-8 weeks	Exercise capacity; HRQoL
ESBY [80,81,82]	Angina pectoris	SCS	Coronary artery bypass surgery	104	6 and 58 months	Angina attacks
SPiRiT[83]	Angina pectoris	SCS	Percutaneous myocardial laser revascularisation	68	12 months	Exercise capacity
Hautvast [84]	Angina pectoris	SCS	Inactive stimulator	25	6 weeks	Exercise capacity

All studies used SCS devices with implantable pulse generator, and non-rechargeable internal battery, none of the studies used SCS devices with radio-frequency system. All studies used SCS devices from Medtronic, with the majority using Itrel II or III systems. Four of the studies had 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 for 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 test stimulation received permanent SCS implant (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 as paraesthesia coverage is usually easier to achieve for ischaemic rather than neuropathic pain. Three of these trials (PROCESS, Kemler, Claeys) included ITT analyses. For the Claeys trial this would be the same as a per treatment analysis as there were no test failures. The PROCESS and Kemler trials patients reported analyses that analysed patients allocated to SCS in the SCS group regardless of whether the patient passes or failed test stimulation or received permanent implant. This indicates that the inclusion of test stimulation in trials was unlikely to skew the results in favour of SCS.

As can be seen from Tables 1 and 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 due to 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-analysis.

All included studies were prospective randomised controlled trials. 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.

Most of the outcome measures used by the included trials have been validated:
VAS[19] (as mentioned in section 3.1, validity is not universally acknowledged for chronic pain, may be more applicable to acute pain); McGill Pain Questionnaire;[89] Medication Quantification Scale;[90] Jebsen functional test for the hand;[91] Kemler functional test for the foot;[92] Oswestry Disability Index;[93] Bruce protocol exercise test[94]; 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;[95] Seattle Angina Questionnaire;[33] Quality of life questionnaire Angina Pectoris QLQ-AP;[34] and the Self-Rating Depression Scale.[96]

Details of quality assessment are presented in Appendix 5.
Inadequate methods of random assignment, allocation concealment, excluding participants from analysis and lack of blinding can lead to over-estimating of treatment effect.[97] Method of randomisation was reported and adequate in 5 trials (PROCESS, North, Kemler, ESES, SPiRiT). Allocation concealment was reported and adequate in 5 trials (PROCESS, Kemler, ESES, deJongste, SPiRiT).

All trials presented statistical analyses in which patient data were included according to allocated treatment, rather than received treatment, in accordance with the intention-to-treat principle. Most trials presented intention-to-treat 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 as the authors stated it did not alter 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 randomised in 6 of the trials (PROCESS, North, Kemler, ESES, Jivegard, SPiRiT), although some of these later became underpowered (ESES, Jivegard).[98] 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 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. 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.[99]

5.2.2 Clinical effectiveness in neuropathic pain

Two RCTs were available for FBSS and one RCT for CRPS (sections 5.2.2.1 and 5.2.2.2). These trials were designed to assess pain relief.

Systematic reviews identified case series for neuropathic conditions other than FBSS and CRPS. Taking into account 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] postherpetic neuralgia,[48] chronic low back pain,[52] chronic back and leg pain,[49] FBSS,[49] CRPS I and II.[48,50,51] A review by Taylor *et al.* found greater treatment effects of SCS were reported by case series of poorer quality and shorter duration.[49]

5.2.2.1 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 cross-over to the other treatment group. In both trials, SCS was additional 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 6.1.

FBSS pain outcomes

Table 3 Pain outcomes FBSS

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)	Odds Ratio 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

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 SCS and reoperation groups (North).

FBSS Medication outcomes

Table 4 FBSS 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

As shown in Table 4, there was no difference between SCS and CMM groups in opioid use, morphine equivalent dose or NSAIDS, or antidepressants (borderline significance p=0.06) (PROCESS). Significantly fewer SCS than CMM patients were taking anticonvulsants at 6 months (p=0.02) (due to 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 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.

FBSS Functional outcomes

Table 5 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 -21.2to -1.3) SCS group showed a significantly greater improvement in function compared with CMM patients (p = 0.0002).

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 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 note that not all patients whose treatment was classified as not successful opt to crossover.

FBSS HRQoL outcomes

The PROCESS trial assessed HRQoL with 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 health. There was a significant difference between groups in 7 out of 8 domains $p<=0.02$, but not in Role physical.

Table 6 FBSS HRQoL outcomes

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis)	SF-36 SCS group	SF-36 control group	Comparison
PROCESS	6 months	50	44	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	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	difference in means (99%CI) sig diff for: Physical function 16.3 (5.3 to 27.2) p<0.001; Bodily pain 13.4 (3.9 to 23.0) p<0.001; General health 11.5 (minus1.2 to 24.1) p<0.001; Vitality 10.2 (minus1.4 to 21.7) p=0.01; Social functioning 15.7 (2.1 to 29.4) p= 0.002; Role-emotional 21.8 (minus1.4 to 45.0) p=0.02; Mental health 12.5 (0.1 to 24.8) p=0.002; nonsig between groups Role-physical 9.5 (minus5.9 to 24.9) p=0.12

FBSS summary

Evidence from FBSS trials suggested 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.

5.2.2.2 Clinical effectiveness in complex regional pain syndrome

One RCT (Kemler) included patients with CRPS type 1. Compared SCS plus physical therapy (PT) with PT alone. Details of the trial are presented in Appendix 6.2. The trial had adequate randomisation and allocation concealment and reported an ITT analysis.

CRPS Pain outcomes

Table 7 CRPS 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 2.4cm	increase of 0.2cm	p<0.001
Kemler	2 years	35	16	reduced by 2.1cm (SD 2.8)	no change 0cm (SD 1.5)	p=0.001
Kemler	5 years	31	13	reduced by 1.7cm	reduced from baseline by 1.0cm	p=0.25

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 due partly to a lower pain reduction in the SCS group and partly to a reduction in pain in the PT group at longer follow-up.

The Kemler trial also measured Global Perceived Effect (GPE), a 7-point scale, finding significantly more patients SCS than PT patients considered they were "much improved" at 6 months ($p=0.01$), and at 2 years ($p=0.001$). This difference also was significant in a per treatment analysis at 6 months and 2 years ($p<0.001$). A review by Grabow calculate the number needed to treat to obtain at least one patient with 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 GPES or a 50% or more decrease in pain measured by VAS, 20 of 35 SCS patients achieved success at 2 years.[67]

CRPS Functional outcomes

Table 8 CRPS 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=14 for foot	n=11 for hand; n=6 for foot	hand function mean 2 (SD 10); foot function mean -1sec (SD 3)	hand function mean -1 (SD 5); foot function mean -1sec (SD 3)	hand function p=0.21; Foot function p=0.96
Kemler	2 years	n=21 for hand; n=14 for foot	n=10 for hand; n=5 for foot	hand function mean 2sec (SD 14); foot function mean -3 sec (SD4)	hand function mean -5degrees (37); foot function mean -5sec (SD5)	hand function p=0.78; Foot function p=0.48

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 6.2). 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.

CRPS HRQoL outcomes

HRQoL outcome measures cited by Kemler were Nottingham Health profile, Euroqol 5D, short version of Sickness Impact Profile, and Self-rating Depression Scale. There were no differences in HRQoL between groups in any ITT analysis (Table 9). A per treatment analysis at 6 months, and at 24 months, suggested 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 foot (P=0.008).

Table 9 CRPS HRQoL outcomes

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

CRPS summary

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

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

5.2.3 Clinical effectiveness in ischaemic pain

Four RCTs were available for CLI (section 5.2.3.1) and 4 RCTs for angina (section 5.2.3.2). Only 1 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 (section 5.2.2) 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]

5.2.3.1 Clinical effectiveness in critical limb ischaemia

Four CLI trials were included. Although trials did not explicitly state pain duration, they were included as stage of disease indicated 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 6.3). 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 prior vascular leg surgeries.

CLI 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 the pain-rating index of the McGill 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 month 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 month or 12 months follow-up. Skin temperature in the ischaemic area, measured by VAS, didn't differ between 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 than the CMM group, whereas in the case of amputation pain relief slightly favoured CMM.

Table 10 CLI 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 by 1.35cm	reduction by 2.57cm	nonsig
ESES	12 months	42	38	reduction by 1.94cm	reduction by 2.15cm	nonsig
ESES	18 months	27	24	reduction by 2.45cm	reduction by 2.61cm	nonsig

CLI medication outcomes

ESES found a reduction in numbers of patients taking narcotics in SCS and CMM groups (Table 11). ESES used a Medication Quantification Scale (MQS) 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 nonsignificant 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.

Table 11 CLI medication outcomes

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

CLI Functional outcomes

All 4 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[98] including the studies ESES, ESES pilot, Suy, Jivegard and Claeys, produced a nonsignificant 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[87] included a non-randomised trial (Amann[100]) in a meta-analysis of limb salvage at 12 months which indicated significantly greater limb salvage of SCS

compared with control, however excluding the non-randomised trial found a nonsignificant difference between SCS and control RR 0.78 (95%CI 0.58 to 1.04), RD 0.09 (95%CI -0.01 to 0.19).

Systolic toe to brachial pressure index did not differ between 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 (ABI), with neither group differing from baseline. For the ABI Claeys found the mean change for SCS patients was significantly different ($p<0.02$) from the mean change for PGE1 patients at 12 months, although the mean ABI of the SCS patients was not significantly increased. Transcutaneous oxygen pressure (TcpO2) did not differ between SCS and CMM (ESES), but was higher ($p<0.05$) in SCS than PGE1 group at 12 months.

Subgroup analysis of the ESES trial found patients with intermediate skin microcirculation prior to treatment showed a nonsignificant trend for the SCS group to have a lower amputation rate at 18 months follow-up (Appendix Data extraction 6.3]).
Success within subgroups can suggest that selection criteria be employed to decide which patients are more likely to benefit from SCS. Ubbink *et al.* suggest SCS may be more effective for CLI patients if they have a TcpO2 between 10 and 30 mmHg.[101] The systematic review by Ubbink[87] included a non-randomised trial[100] that suggested patients with adequate TcpO2, pain relief and paraesthesia coverage in response to test stimulation, benefited significantly more from SCS than conventional treatment. Subgroup analysis for the Jivegard trial, in surviving patients without arterial hypertension, found significantly ($p=0.045$) lower amputation rate in SCS group than Analgesics group. On a different outcome, the Claeys trial suggested better response to SCS of patients with TcpO2 >10mmHg in terms of ulcer healing.

Table 12 CLI 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%	nonsig
ESES	12 months	60	60	24 (from rm143)	29 (from rm143)	60%	46%	nonsig
ESES	24 months	60	60	Major amputation n=25	major amputation n=29	52%	46%	nonsig between groups p=0.47, HR for SCS vs control group =0.81(0.47-1.51)
ESES pilot	12 months	19	18			67%	47%	Nonsig p = 0.082 hazard ratio 2.3
ESES pilot	24 months	19	18			61%	39%	nonsig 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, nonsig between groups p=0.42

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
Jivegard	18 months	25	26	9 amputations, of which 1 major amputation	14 amputations, of which 6 major amputations	62%	45%	nonsig 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%)			nonsig for minor and major amputations

CLI HRQoL outcomes

One of the trials, ESES, assessed HRQoL (Table 13). There was no significant difference between SCS and CMM on NHP (significant reduction in NHP pain score for both groups), EuroQol, 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.

Table 13 CLI HRQoL 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 (SE2.6) (from baseline overall NHP mean 48 (SE2.6))	overall NHP mean 34 (SE3) (from baseline overall NHP mean 47 (SE2.6))	overall NHP nonsig
ESES	18 months	27	24	overall NHP mean 35 (SE2.6) (from baseline overall NHP mean 48 (SE2.6)). NHP Pain Score 31 (SE=6) significant reduction from baseline (baseline 70 (n=57, SE 3.9))	overall NHP mean 34 (SE3) (from baseline overall NHP mean 47 (SE2.6)). NHP Pain Score 36 (SE=6), significant reduction from baseline (baseline 72 (SE 3.5))	overall NHP nonsig. NHP pain nonsig between groups

CLI summary

Evidence from CLI trials suggests SCS was more effective than CMM in reducing 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 PGE1. SCS and CMM were similarly effective in improving HRQoL.

5.2.3.2 Clinical effectiveness in 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 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 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.

Angina 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 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 by 1.1cm	reduction by 0.2cm	nonsig

Angina Medication outcomes

Three trials (deJongste, ESBY, Hautvast) investigated nitrate consumption and all found significant difference between SCS and control group (Table 15). DeJongste found a greater reduction ($p<0.05$) in glyceryl trinitrate (GTN) 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).

Table 15 Angina medication outcomes

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis) NB different comparators	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), sig 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) nonsig 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) sig reduction from baseline p<0.0001	Nitrate consumption, doses/week baseline 13.7 (12.1) 6 month follow-up 3.1 (8.7) sig reduction from baseline p<0.0001	Nonsig between groups for consumption of short-acting nitrates. sig more reduction for control, than for SCS group, for long-acting nitrates p<0.0001
Hautvast	6 weeks	13	12	Nitrogen consumption (tablets) 1.6 ± 2.2, sig diff from baseline, difference (%) minus48 ± 49 p=0.01 (baseline 3.6 + 2.8)	Nitrogen consumption (tablets) 2.6±1.7, nonsig from baseline difference(%) 27±63 (baseline 2.3±1.6)	p=0.03

Table 16 Angina functional outcomes Angina attacks/class

Trial	Follow-up	No. in SCS group (in analysis)	No. in control group (in analysis) NB different comparators	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) sig 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) nonsig from baseline (baseline 16.5 (95%CI 9.0-23.9))	p<0.05
ESBY	6 months	49	36	Angina attack frequency, attacks/wk mean 4.4 (SD7.4) sig reduction p<0.0001 (baseline mean 14.6 (SD 13.5),)	Angina attack frequency, attacks/wk mean 5.2 (SD 10.3) sig reduction p<0.0001 (baseline mean 16.2 (SD 12.6))	nonsig
Hautvast	6 weeks	13	12	Angina attacks (per day) 2.3 ± 1.9, sig diff from baseline difference(%) -41 ± 44 p=0.01 (baseline 4.3 ±	Angina attacks (per day) 3.2±1.5, difference from baseline (%) 33±82 (baseline	p=0.01

Trial	Follow-up	No. in SCS group (in analysis)	No. in control group (in analysis) NB different comparators	Frequency angina SCS group	Frequency angina control group	Comparison
				2.4)	2.9±1.4)	

Three of the trials (deJongste, ESBY, Hautvast) assessed 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 (CCS) angina scale. No difference was found at 12 months between SCS and PMR groups in an analysis treating deaths and dropouts as failures, although an analysis excluding patients without follow-up indicated the SCS group had greater improvement in CCS class ($p=0.042$).

Table 17 Angina functional outcomes Exercise tests

Trial	Follow-up	No. in SCS group (in analysis)	No. in control group (in analysis) NB different comparators	Exercise duration SCS group	exercise duration control group	exercise time to angina SCS group	exercise time to angina control group	Comparison
deJongste	6-8 weeks	8	9	mean (SE) baseline 659 (+/- 121), 6-8 weeks 827 (+/-138), change p<0.05	mean (SE) baseline 705 (+/-136); 6-8 weeks 694 (+/-67)	mean (SE) baseline 520 (+/-138), 6-8 weeks 691 (+/-174), change p<0.05	mean (SE) baseline 380 (+/-78), 6-8 weeks 438 (+/-91)	Exercise duration p<0.03 Time to angina p<0.05
SPiRiT	3 months	32	33	mean (SE) 7.33 (0.62)	mean (SE) 7.32 (0.66)	mean (SE) 7.31 (0.73)	mean (SE) 6.26 (0.65)	Exercise duration nonsig p=0.353 Time to angina p=0.028
SPiRiT	12 months	30	30	mean (SE) 7.08 (0.67)	mean (SE) 7.12 (0.71)	mean (SE) 7.31 (0.73)	mean(SE) 6.86 (0.82)	Exercise duration nonsig p= 0.466 Time to angina nonsig p=0.191
Hautv	6 weeks	13	12	(seconds)	(seconds)	(seconds) baseline	(seconds) baseline	SCS group, compared with

Trial	Follow-up	No. in SCS group (in analysis)	No. in control group (in analysis) NB different comparators	Exercise duration SCS group	exercise duration control group	exercise time to angina SCS group	exercise time to angina control group	Comparison
ast				baseline 453±156, 6 weeks 533 ± 184, difference (%) 19±24 change p=0.03	baseline 447±214, 6 weeks 427 ± 177, difference (%) -0.2±17	250±67, 6 weeks 319±85, difference (%) 39±59 change p=0.03	287±119, 6 weeks 246±97, difference (%) -9±21	control, exercise duration was increased (p=0.03), together with time to the onset of angina (p=0.01)

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 SCS than No SCS group ($p<0.03$) (deJongste), and in SCS than Inactive stimulator ($p=0.03$) (Hautvast), but there was no difference between SCS and PMR (SPiRiT). Exercise testing of time to angina was significantly more improved in SCS than 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 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 effectiveness (ESBY authors had reported in a prior case series of angina patients that SCS when switched on could improve exercise training[102]). The exercise test in the ESBY trial found that at 6 months CABG had a significantly greater increase in maximum workload capacity than SCS ($p=0.02$).

Angina HRQoL outcomes

All four trials evaluated HRQoL, all using different outcome measures. deJongste assessed Daily activity score and Social activity score which 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 Short Form 36 at 3 and 12 months (SPiRiT). Hautvast found no difference between SCS and Inactive 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).

Table 18 Angina HRQoL outcomes

Trial	Follow-up	Number of participants in SCS group (in analysis)	Number of participants in control group (in analysis) NB different comparators	HRQoL SCS group	HRQoL control group	Comparison
deJongste	6-8 weeks	8	9	Daily activity score (ADL) median 2.06(95%CI1.65-2.26) sig improved from baseline p<0.008 (baseline median 1.37 (95%CI 1.15-1.67)). Social activity score (SAS) median 2.10 (1.61-2.44) sig improvement from baseline p<0.005 (baseline 1.28 (95%CI 0.99-1.69))	Daily activity score (ADL) median 1.25(95%CI1.10-1.71) nonsig from baseline (baseline median 1.24 (95%CI 1.06-1.50)) . Social activity score (SAS) median 1.39 (1.10-1.65) nonsig from baseline (baseline 1.30 (95%CI 0.60-2.00))	Daily activity score (ADL) sig diff between change in SCS group vs change in control group p<0.05. SAS sig diff between change in SCS group vs change in control group p<0.05.
Hautvast	6 weeks	13	12	Linear Analogue Self Assessment (LASA) scale (cm) 6.8± 1.0, difference (%) 15± 19 sig diff from baseline p=0.01 (baseline 6.0±0.8)	Linear Analogue Self Assessment (LASA) scale (cm) 6.2± 1.1, difference (%) 1± 15 nonsig from baseline (baseline 6.4±1.7)	nonsig

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 ($p<0{\cdot}001$) 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.

Angina summary

Evidence from Angina trials suggested 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.

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.

5.2.4 Complications and adverse events

Numbers of reported SCS device-related complications are shown in Table 19. SCS device-related complications included electrode migration, lead fracture, loss of paraesthesia, dural puncture and infection (Appendix 6). The deJongste trial had no complications during the study period, but during follow-up, when both groups had SCS, there were 2 (12%) patients with lead displacements requiring surgery.

Among the total of 403 implanted patients across all trials, there were 4 (1%) device removals required, all due to 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 2 trials with under 2 months follow-up), which may be due to differences in follow-up period, populations or clinical settings.

Table 19 SCS device-related complications

Trial	Indication	Follow-up	Number of participants given SCS	no. patients with device related event	total device-related complications (some patients more than 1 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%)	1 removed and replaced (due to infection)
Kemler	CRPS	6 months	24	6	13 (11 + 2 dural puncture)	6 (5 + 1 removed) (28%)	1 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 + 1removed) (15%)	1 removed and replaced (due to infection)
Jivegard	CLI	18 months	22	1	1	1 (5%)	
Claeys	CLI	12 months	45		3	3 (7%)	

Trial	Indication	Follow-up	Number of participants given SCS	no. patients with device related event	total device-related complications (some patients more than 1 event)	surgery required to resolve	removal of SCS required
deJongste	Angina	6-8 weeks	8	0		(0%)	
ESBY	Angina	6 months	57			4 (3 + 1 removed) (7%)	1 (due to infection)
SPiRiT	Angina	12 months	32		26	6 (19%)	
Hautvast	Angina	6 weeks	13	0		(0%)	

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 PGE1 but didn't 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 nonfatal) between SCS (n=8) and CABG (n=14), although there were significantly (p=0.03) more cerebrovascular events in the CABG group (8 events) than in the SCS group (2 events).[80]

Table 20 Adverse events (non-SCS device-related)

Trial	Indication	Follow-up	No. given SCS	No. given control treatment NB different comparators	AEs SCS (non-device related)	AEs control
PROCESS	FBSS	12 months	84	44	Number of patients experiencing one or more non-device related event 18 (35%). Patients with 1 or more drug adverse event 2 (4%); Drug adverse events 2; Patients with 1 or more event of extra pain 0 (0%); Events of extra pain 0; Patients with 1 or more new illness/injury/condition 13 (25%); Events of new illness/injury/condition 16; Patients with 1 or more worsening of pre-existing condition 7 (13%); Events of worsening of pre-existing condition 7	Number of patients experiencing one or more non-device related event 25 (52%). Patients with 1 or more drug adverse event 10 (21%); Drug adverse events 12 ; Patients with 1 or more event of extra pain 2 (4%) ; Events of extra pain 2 ; Patients with 1 or more new illness/injury/condition 11 (23%) ; Events of new illness/injury/condition 13 ; Patients with 1 or more worsening of pre-existing condition 7 (15%) ; Events of worsening of pre-existing condition 10

Trial	Indication	Follow-up	No. given SCS	No. given control treatment NB different comparators	AEs SCS (non-device related)	AEs control
ESES	CLI	18 months	59	60	side effects occurred in four patients: duodenal perforation (1), nausea (2), and pruritus (1).	side-effects were reported in ten patients: upper gastrointestinal bleeding (3), nausea (7), dizziness (2).
SPiRiT	Angina	12 months	32	33	30 events	23 events in the control group were categorized as unrelated to the procedure. (An additional 4 events were related to the PMR procedure)

5.3 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 suggests SCS is effective for pain relief in the neuropathic pain conditions 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 was similar for 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. For CRPS, SCS was more effective than PT in reducing pain at 6 months and 2 years, but not at 5 years, and more successful in terms of patients' Global Perceived Effect 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 analgesics 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 analgesics treatment, or PGE1. 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 similarity 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 size 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. HRQoL was more improved by SCS than No SCS. Exercise testing suggested 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 4 (1%) device removals required, all due to 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 implant, and in the case of the FBSS trial patients failing test stimulation but receiving 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 prior to trial participation and that these therapies had been unsuccessful.

Unclear randomisation and allocation concealment, and exclusion of participants from analysis are associated with over-estimation 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 method of randomisation, but allocation concealment was unclear and not all randomised participants were included in

analysis. 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 suggests that SCS is effective for the relief of neuropathic pain in FBSS and CRPS. There may be additional benefit 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 than CMM up to 6 months which 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 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 suggests SCS could be effective in other forms of neuropathic pain, and it may be effective in a subgroup of 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.

6. ASSESSMENT OF COST-EFFECTIVENESS

6.1. 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.

6.1.1 Search strategy

Studies were identified through searches of MEDLINE (1996-present), EMBASE (from 1996), Cochrane Database of Systematic Reviews (CDSR), and the 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.

6.1.2 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)
- The benefits were estimated in terms of cost per life-years saved (LYS) or cost per quality adjusted life years (QALYs)
- Adult populations
- The study was published in English

Exclusion criteria

- Studies that adapted published evaluations for other settings
- Studies that do not report results in terms of ICERs

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.

6.1.3 Quality assessment strategy

The quality of studies was assessed using a combination of key components of the British Medical Journal checklist for economic evaluations[103] together with the Eddy checklist on mathematical models employed in technology assessments.[104]

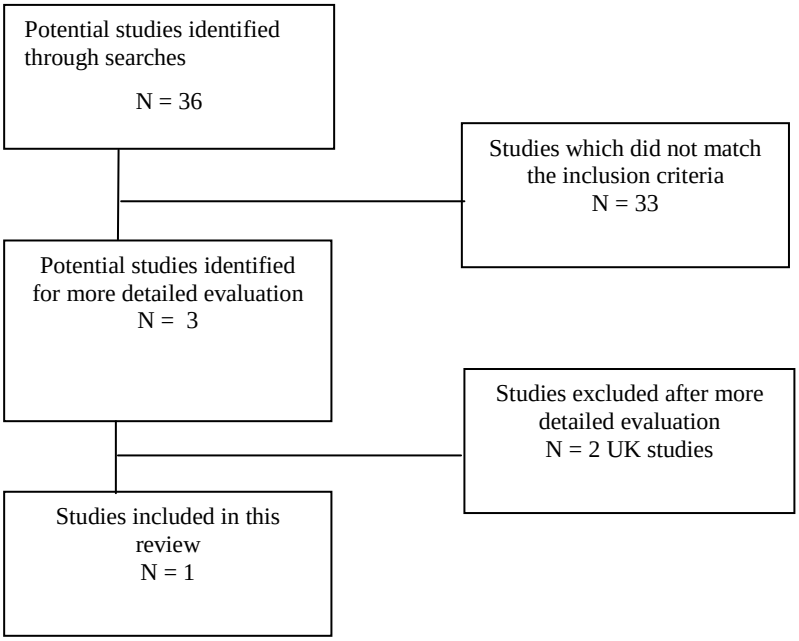
6.1.4 Results of review

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 only. Three UK studies were identified at this stage. More detailed evaluations revealed 2 of the potential UK studies did not estimate benefits in terms of life years saved or quality adjusted life years and therefore failed the inclusion criteria. These 2 UK studies reported physical functioning, drug use, and work status and hence were retained for information. Only one UK study satisfied all 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 Great Britain pounds using the Gross Domestic Product Purchasing Power Parities,[105] and results are adjusted to 2007 using the Pay and Prices annual percentage increase.[106]

Figure 2: Studies eliminated/selected for the review after applying inclusion/exclusion criteria



Published cost effectiveness analysis

Taylor RJ, and Taylor RS. Spinal cord stimulation for failed back surgery syndrome: A decision analytic model and cost-effectiveness analysis. International Journal of Technology Assessment in Health Care 2005; 21(3):351-8.[107]

This study evaluated the cost effectiveness of SCS compared to conventional nonsurgical treatment in patients with FBSS. A European healthcare 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 6% and benefits at 1.5%, according to NICE guidance at that time.[108]

The model had two stages, a decision tree and a Markov model. The decision tree examined the costs and outcomes of SCS and 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 a SCS implant whilst 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 basecase 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 (cost less and accrued more benefits) in both basecase and one-way sensitivity analyses.

6.2 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 spinal cord stimulation 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.

6.2.1 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 six-months) and a Markov process post six months and up to 15 years. Six mutually exclusive health states are defined: optimal pain relief with no complications, optimal pain relief with complications, sub-optimal pain relief with no complications, sub-optimal pain relief with complications, no perceived pain relief and death due to all cause of mortality (more details in Appendix 8).

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.[109]

Populations considered in the model

The following three population groups are used:

FBSS

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

FBSS

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

CRPS

- 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 six months and that 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 5cm on a visual-analogue scale from 0 cm (no pain) to 10 cm (very severe pain).

Comparators used in the model

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

Comparator 1: conventional medical management (CMM)

The CMM comprises drug therapy and non-drug therapy. The drug therapy basically consists of opioids, 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: re-operation

Re-operation is defined as lumbosacral spine surgery. Re-operation patients also receive CMM.

Clinical parameters

FBSS: Short-term clinical data

Costs of health states, monitoring and treatments in the model

The costs of conventional medical management are taken from the PROCESS study,[59] which reported data based on a follow-up of six months. It is assumed that the annual cost of CMM in year two is reduced by 13.5% compared to the cost of year one. This assumption was taken from a five year analysis of cost for CMM in Canada.[110]

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 over the first six months	£1,692	£2,664
Average cost of non-drug treatment over the first six months	£28	£804
Average cost of CMM in year one	£3,439	£6,936
Average cost of CMM (years 2 to 15)	£3,439	£6,000

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

Table 22 Additional costs for patients who undergo SCS

Average cost per screen	£4,069	
Average cost of device implant	£11,269	
Average cost of failed screening	£1,800	
Average cost of device explant	£1,800	
Average cost of re-implant	£11,190	
	Initial implant	Re-implant
Cost of adverse events over 6 months	£622	£530
Adverse events (subsequent cycles)	£95	£95

For FBSS patients that undergo revisional spinal surgery, it is assumed that the CMM cost is the same as 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 the patients that undergo CMM alone. The cost of revisional surgery of £4,252 is taken from the NHS National Tariff R09.[111]

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

Utilities used in the model

As per NICE recommendations,[109] the health state quality of life utilities are based on the EQ-5D administered within the PROCESS trial.[59] The baseline utility value for all patients is 0.168.

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
Sub optimal pain relief	0.258
Sub optimal pain relief + complications	0.258
No perceived pain reduction	0.168

6.2.2 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 (basecase) and with 50% threshold criteria, the ICERs for FBSS and CRPS range from £7,954 per QALY (for FBSS:SCS+CMM vs re-operation) to £18,881 per QALY (for CRPS:SCS+CMM vs CMM).

Table 24 Summary of results from the ABHI model

50% pain threshold criteria	Cost Difference	QALYs Difference	ICER
FBSS: SCS+CMM vs CMM alone			
Basecase: 4-year device longevity	£11,439	1.25	£9,155
2-year device longevity			£30,285
7-year device longevity			£2,745
Device longevity > 7 years			SCS+CMM dominates
FBSS: SCS+CMM vs re-operation			
Basecase: 4-year device longevity	£10,651	1.34	£7,954
2-year device longevity			£26,445
7-year device longevity			£2,362
Device longevity > 7 years			SCS+CMM dominates
CRPS: SCS+CMM vs CMM alone			
Basecase: 4-year device longevity	£12,041	0.64	£18,881
3-year device longevity			£28,015
10-year device longevity			£1,607
Device longevity > 7 years			SCS+CMM dominates

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 vs re-operation) to £36,393 per QALY (for CRPS:SCS+CMM vs CMM).

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			
Basecase: 4-year device longevity	£11,621	1.06	£10,962
2-year device longevity			£35,921
7-year device longevity			£3,405
Device longevity > 7 years			SCS+CMM dominates
Maximum failure rate per annum on basecase	£10,126	0.58	£17,463
FBSS: SCS+CMM vs re-operation			
Maximum failure rate per annum on basecase	£9,121	0.62	£14,726
CRPS: SCS+CMM vs CMM alone			
Maximum failure rate per annum on basecase	£10,734	0.29	£36,393

Probabilistic results from the ABHI model

FBSS: SCS+CMM vs CMM

The results of the probabilistic analysis using 15-year horizon suggest that SCS+CMM compared to CMM alone produce more QALYs. The cost effectiveness acceptability curve (ABHI report, Appendix 12 pg 117) shows that when using a threshold of £20k per QALY the probability of SCS+CMM being cost effective is around 80%. Additionally, at a £30k per QALY threshold, this probability is over 95%.

FBSS: SCS+CMM vs re-operation

The results found in the probabilistic analysis using 15-year horizon suggest that SCS+CMM compared to re-operation produce more QALYs. The cost effectiveness acceptability curve (ABHI report, Appendix 13 pg 121) shows that when using a threshold of £20k per QALY the probability of SCS+CMM being cost effective is higher than 90%. Additionally, at a £30k per QALY threshold, this probability is around 98%.

CRPS: SCS+CMM vs CMM alone

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

6.3.2 Critique of the ABHI model

A full review of the model is described in Sections 6.2.1 and 6.2.2. The quality of model was assessed using a combination of key components of the British Medical Journal checklist for economic evaluations[103] together with the Eddy checklist on mathematical models employed in technology assessments and presented in Appendix 7.[104] The model structure is suitable and is based on the Taylor and Taylor economic model.[107] The model is evidence based and appropriate to answer the research question. The results are presented in incremental costs effectiveness ratios and sensitivity analyses including additionally, probabilistic sensitivity analysis were performed.

6.3 Independent economic assessment by ScHARR

6.3.1 Objective

The primary objective of this evaluation is to appraise the cost effectiveness of the use of spinal cord stimulation in patients with neuropathic or ischaemic pain.

6.3.2 Methods

6.3.2.1 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 six 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.*, that presents a Kaplan-Meier survival curve that illustrates subsequent gradual loss of pain control during a 15 year period.[112] Taylor and Taylor first used this model structure, to evaluate the cost effectiveness of SCS compared to CMM.[107] Published RCT data are used to determine the treatments' efficacy and the results are presented in terms of incremental cost effectiveness ratios (ICERs).

Population considered in the ScHARR economic evaluation

The model evaluates the cost effectiveness of treatment in the three following populations:

1) Adult patients (>18 years) 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 vs. CMM).

Their pain intensity is of at least 50 mm on visual analogue scale (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.

2) Adult patients (>18 years) 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 surgical remediable compression or critical cauda equina compression. This patient population represents that of the North trial[62] (SCS vs. re-operation).
3) Patients with CRPS are based on the Kemler trial[65] (SCS vs CMM). Patients are adults (> 18 years) 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 visual analogue scale (0 mm represents no pain and 100 mm represents very severe pain). Patients are excluded if they suffer Raynaud's disease, neurologic 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 (CMM)

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: re-operation

Re-operation is defined as lumbosacral spine surgery. Re-operation 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 a short-term period of time. A Markov model is used to explore the clinical pathway of individuals suffering from FBSS or CRPS in a long-term period of time. 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 cost 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 in 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 due to the increased uncertainty this would cause.[112]

Decision tree health states modelled

The first stage of the model (first six months) is defined with four possible health states: a) optimal pain relief with no complications, b) optimal pain relief with complications, c) sub-optimal pain relief with no complications and d) sub-optimal pain relief with complications. It is assumed that the patients do not change therapy during the first six months of treatment. The decision tree is populated with data from the Kumar *et al.* (PROCESS), North *et al.* and Kemler *et al.* RCTs.[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).

Figure 3: Six-month decision tree for SCS+CMM vs CMM in FBSS and CRPS

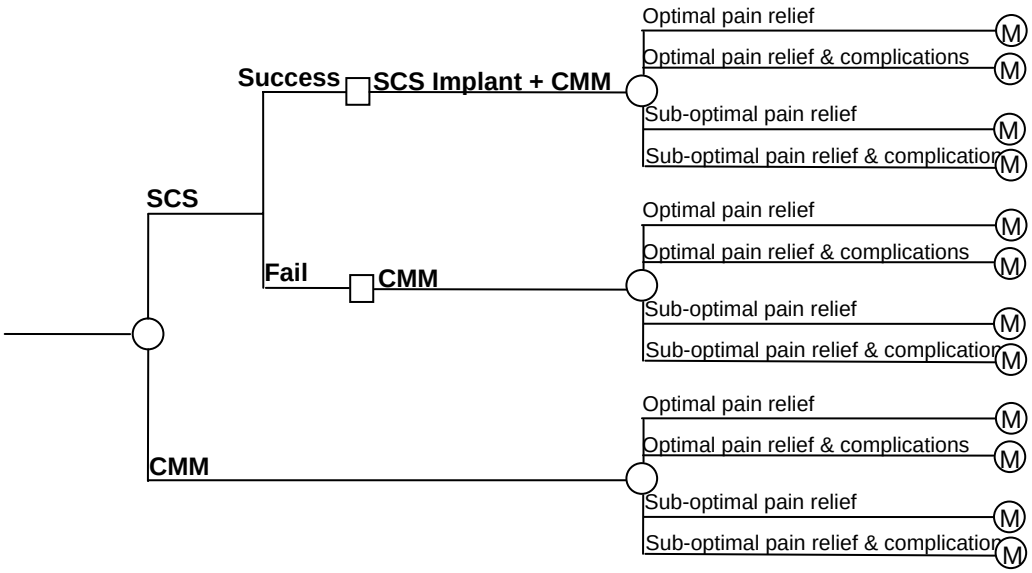
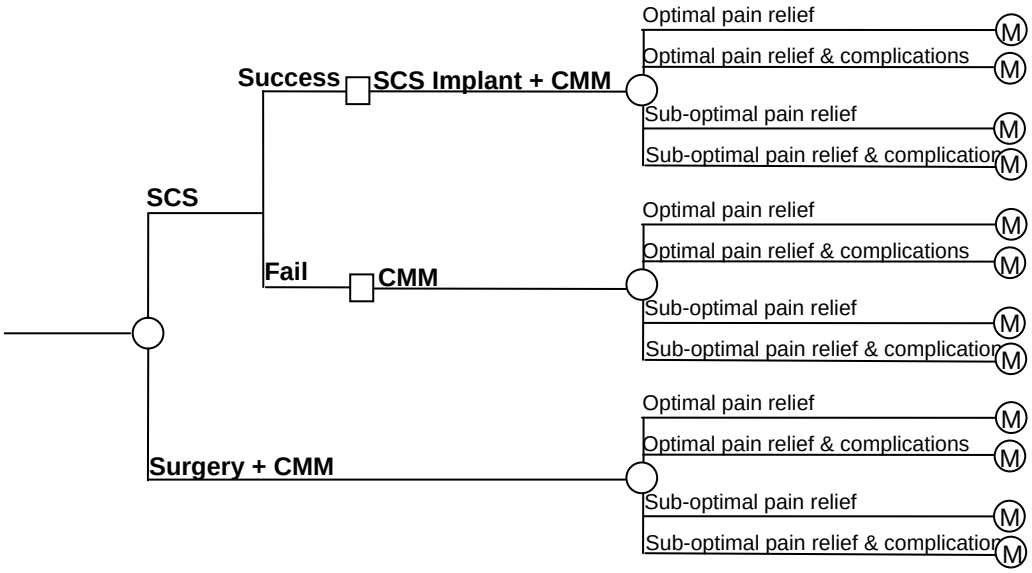


Figure 4: Six-month decision tree for SCS+CMM vs re-operation in FBSS



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: a) optimal pain relief (includes patients with or without complications), b) sub-optimal pain relief (includes patients with or without complications), c) no pain relief (SCS), d) no pain relief (Surgery), and e) dead all causes. For CRPS, there are four possible health states: a) optimal pain relief (includes patients with or

without complications), b) sub-optimal pain relief (includes patients with or without complications), c) no pain relief (SCS), and d) dead all causes. It is assumed that all patients are in the same health state they were at the time of the decision tree when entering the Markov model. During each three month cycle of the model a proportion enter one of the health states defined in figures 5 and 6.

Figure 5: Schematic of the long-term Markov Model for FBSS

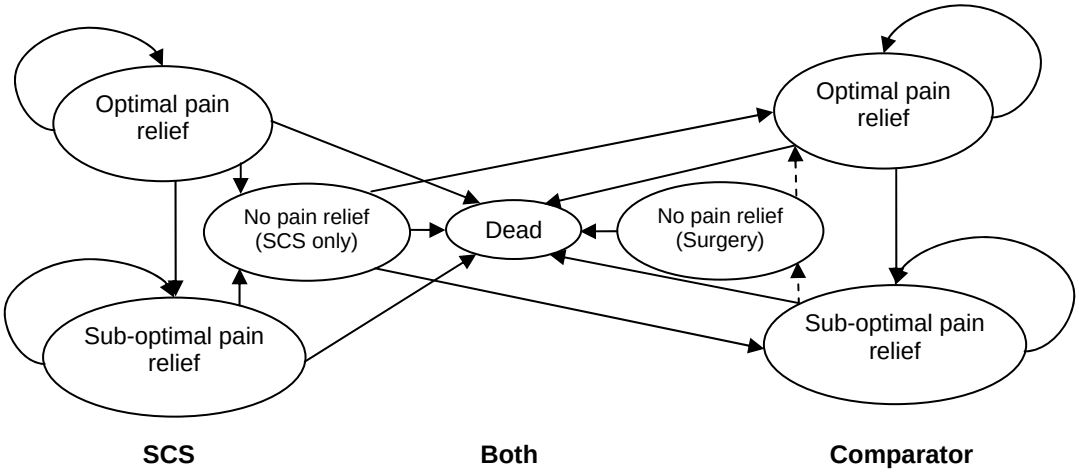
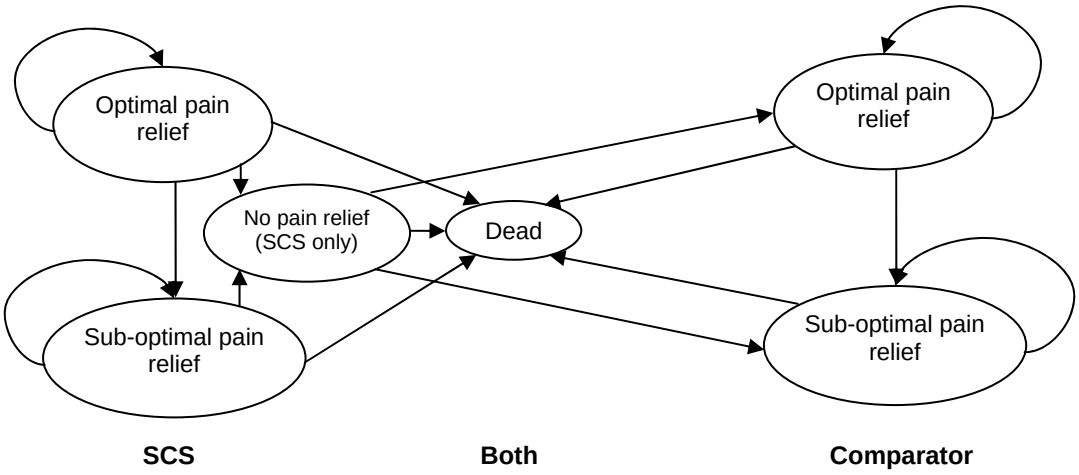


Figure 6: Schematic of the long-term Markov Model for FBSS



Optimal pain relief is defined as having at least 50% pain reduction from baseline, measured by a VAS. Sub-optimal pain relief is defined as having less than 50% pain reduction from baseline, measured by a VAS.

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.[109] Costs are at 2007 prices**.**

Probabilities of levels of pain relief

Short-term model

The probabilities of events for the six-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 5. 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: 1) for FBSS: SCS+CMM vs. CMM, the PROCESS trial[59], 2) for FBSS: SCS+CMM vs re-operation, the North trial[62], and 3) CRPS: SCS+CMM vs CMM, the Kemler trial.[65]

In the FBSS: SCS+CMM vs. 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.

Table 26 Six-month success probabilities

FBSS: SCS vs. CMM		**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**
PROCESS	SCS (n=52)	43	0.827 (43/52)	24	0.585 (24/41*)
	CMM (n=48)	NA	NA	4	0.091 (4/44**)
* From 43 successful trial participants 2 withdrew consent ** From 48 patients 4 withdrew consent					
FBSS: SCS vs Re-operation		**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**
North	SCS (n=23)	17	0.739 (17/23)	17	1.00 (17/17)
	Re-operation (n=26)	NA	NA	12	0.462 (12/26)
CRPS: SCS vs. CMM		**Number of successful participants after SCS screening trial**	**Probability of screening trial success**	**Number of patients that achieved ≥ 50% pain relief**	**Probability of achieving ≥ 50% pain relief**
Kemler	SCS (n=36)	24	0.667 (24/36)	18	0.750 (18/24)
	CMM			No-reported	0.444 assumed

Long-term model

As in Taylor *et al*., it is assumed that after six-months 18% of complications in SCS occur per annum.[49] According to the 22 year follow-up SCS study conducted by Kumar *et al*., complications were due to fractured electrode, displaced electrode, hardware malfunction, biological, and infection costs.[112] 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.[113] 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*. reported an annual SCS withdrawal rate of 3.24%.[112] The main reason for SCS withdrawal was due to the device failing to provide any pain relief.

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 trial1[114] are academic in confidence and therefore resource use evidence is taken from other sources as outlined below. Medication costs are taken from the 2007 BNF,[115] costs for GP visits are taken for Curtis and Netten,[106] 2007, 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.[116] The unit prices are substituted with UK costs obtained from the NHS reference costs and from Curtis and Netten.[117] The consultation cost consists of psychiatrist, social worker, general practitioner (GP), neurosurgeon, neurologist, orthopaedic surgeon and follow up during trial (nurse) costs. The investigation cost consists of CT, MR imaging, radiography, and myelography. The surgery cost is based on anaesthesia, and neurosurgical fees. The estimated total cost per patient for SCS trial is £4,156.

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.[116] The estimated implantation cost per patient is £10,479.

Complications: The cost for complications is calculated based on fractured electrode, displaced electrode, hardware malfunction, biological, and infection costs, taken from Kumar *et al*.[116] and adjusted to 2007 £s using Pay and Prices annual percentage increase.[106] 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*. where each patient visits the GP twice, one initial visit and one follow up visit, has a neurosurgical consultation, surgeon's fee, and hospital charges.[116] The estimated explantation cost is £1,041.

Conventional medical management costs

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

Table 27: Drug therapy resource use [59]

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

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

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]
TENS	0%	11%	

a – number of session over 6 months

The costs of physical rehabilitation (£40) and psychological rehabilitation (£40) per hour of client contact are taken from Curtis and Netten, 2007.[106] The cost of acupuncture is taken from Ratcliffe *et al.* and adjusted to 2007 £s.[118] Ratcliffe *et al.* evaluated the cost effectiveness of acupuncture in the management of persistent non-specific low back pain.[118] The estimated unit cost of acupuncture treatment is £31.5. It is assumed that the cost of massage and the cost of acupuncture are the same.

A 5-year Canadian cost effectiveness analysis of treatment of chronic pain with SCS versus CMM showed that the cost of CMM in year two was reduced by 17.8% compared to the cost in year one.[110] This is taken from a clinical study with a control group of 44 patients where resource consumption data were collected. The cost of CMM were calculated using the following parameters: physician fees, drugs, radiological investigations (e.g. computed tomography, x-ray, 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 two is reduced by 17.8% compared to the cost of year one. After year two the cost of CMM remains constant.

Re-operation costs

The re-operation cost is taken from the NHS National Tariff R09 (revisional spinal procedures) £4,252.[111]

CRPS

It is assumed that the drug and non-drug costs for CMM in CRPS are equivalent to those costs for CMM in FBSS.

HRQoL utility by health state

A literature review was carried out to obtain most appropriate and recent published evidence on utility measure 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)[119]
- 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.* investigated the burden of neuropathic pain in a cross-sectional survey.[16] They surveyed 602 patients recruited from general practitioners in six European Countries: France, Germany, Italy, the Netherlands, Spain and the United Kingdom. The population were adult patients (>18 years) with at least a-month history of the condition who had experienced symptoms in the week prior to the survey. The patient questionnaire included the Brief Pain Inventory (BPI), the EQ-5D, and questions productivity, non-drug treatment and physician visits frequency. Most patients reported moderate (54%) or severe (25%) pain. They reported 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 respectively. In this ScHARR economic evaluation, it is assumed that in CRPS for optimal pain relief, the utility value is 0.67, for sub optimal 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 reported a utility loss associated with SCS complication (e.g. infection, electrode or lead problems) as -0.05 utility units.[107] This was applied to both optimal and sub optimal pain relief health states. Table 29 presents the utility values used in this economic assessment.

Table 29 Health state utility values used in the model[59,16]

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

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
- Sub-optimal pain relief is defined as achieving less than 50% of pain relief from baseline, measured by VAS
- No patient dies within the first six months (short term decision tree)
- Patients, when entering the Markov process remain in the same health state (optimal or sub-optimal pain relief) as they were at the end of the first six months (short-term decision tree model).
- It is assumed that patients on CMM do not experience either short-term or long-term complications.[113]
- It is assumed that after six-months 18% of complications in SCS occur 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.[118]
- It is assumed that the annual cost of CMM in year two is reduced by 17.8% compared to the cost of year one.[110]
- After year two 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 of 3.24%.[112]
- The model explores the cost and benefits accrued through pain relief over a 15 year period.[112]
- In FBSS, the utility for 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]

Cost Effectiveness Ratios

Incremental cost effectiveness ratios (ICER) measure the additional cost per QALY gained of Treatment A versus Treatment B:

$$ICER = \frac{\text{Cost Treatment A - Cost Treatment B}}{\text{Utility Treatment A - Utility Treatment B}}$$

6.3.2.2 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 National Health Service 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 conventional medical management (CMM). A threshold analysis is presented due to the dearth of direct clinical evidence. This analysis attempts to clarify the 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 5. This model is also centred on 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 medical management.[120] Consecutive, unselected patients who had coronary angiography between April 1996 and April 1997 at three hospitals of one NHS trust in London were recruited. Four thousand one hundred and twenty one patients were identified and followed for six years. From these patients, a subgroup of 1740 patients was rated to be appropriate to have CABG (n=815), PCI (n=385) or both revascularisation procedures (n=520). Twenty patients were excluded because they died before having revascularisation.

Clinical judgement and available evidence were used to define appropriateness using a nine member Delphi panel.[121] Approximately, 70 % of the 1720 have 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: coronary artery bypass grafting (CABG)

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

Comparator 2: percutaneous coronary intervention (PCI)

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

Comparator 3: conventional medical management (CMM)

The medical therapy basically consists of short-acting nitrates, β-blockers, anticoagulants ACE inhibitors, long-acting nitrates, calcium channel inhibitor and aspirin.[80]

Table 30 presents the distribution of patients in each of the three scenarios and three comparators (management) defined above.

Table 30 Number of patients bay 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

Time horizon

The model explores the cost 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.[109] 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 BNF,[115] costs for GP visits are taken for Curtis and Netten,[106] 2007, and other costs are adjusted to 2007 £s.

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.[116] The estimated implantation cost per patient is £10,479.

Coronary artery bypass grafting: The cost for CABG at six years is taken from Griffin *et al.*[120] and adjusted to 2007 £s using Pay and Prices annual percentage increase.[106] The estimated CABG average costs per patient at six years are presented in Table 31.

Percutaneous coronary intervention: The cost for PCI at six years is taken from Griffin *et al.*[120] and adjusted to 2007 £s using Pay and Prices annual percentage increase.[106] The estimated PCI average costs per patient at six years are presented in Table 31.

Conventional medical management costs

At six years the estimated CMM costs per patient are presented in Table 31. These costs are taken from Griffin *et al.*[120] and adjusted to 2007 £s using Pay and Prices annual percentage increase.[106]

Table 31 Estimated cost for CABG, PCI, CMM and SCS for three scenarios at 6 years[120]

Scenario	Costs 2006/7 (£)*
1. Appropriate for CABG	
CABG	£18,000
PCI	£14,708
CMM	£11,502
SCS	£18,463
2. Appropriate for PCI	
CABG	£17,535
PCI	£12,183
CMM	£9,302
SCS	£16,857
3. Appropriate for both	
CABG	£18,932
PCI	£14,848
CMM	£11,332
SCS	£18,339

* Discounted at rate 3.5% a year

The ESBY trial that compares SCS versus CABG showed that the nitrate consumption on the SCS arm is reduced, after six 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 one. This can be an overestimated assumption since the ESBY trial reports a reduction on the use of nitrates only. The cost of medication remains constant for the five following years.

Health economic outcomes

ScHARR's model includes the following health economic outcomes:

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

HRQoL utility

A literature review was carried out to obtain most appropriate and recent published evidence on utility measure 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)[119]

- UK setting studies are preferred to non-UK studies
- Patients suffering from severe angina

The study by Griffin *et al.*, that investigated the cost effectiveness of clinically appropriate decisions of treatments for angina pectoris presented utilities and QALYs at six years.[120] Patients completed the EQ-5D health related quality of life instrument, from which the utilities scores were derived (Table 32).

Table 32 Health state utility values and QALYs at 6 years used in the model[120]

Scenario	Utility at 6 years	QALYs*
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

* Discounted at rate 3.5% a year

6.3.3 Results

6.3.3.1 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 33. The results are presented in discounted incremental values. The discounted and undiscounted costs and QALYs are provided in Appendix 11. The base case considers a device price of £[redacted]. This price is the middle value from the price list provided by two of the SCS manufacturers presented in Appendix 9.

Table 33 Results using different device longevity values

	ICER (£/QALY)		
Device Longevity (years)	**FBSS:SCS+CMM vs CMM**	**FBSS:SCS+CMM vs Re-operation**	**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	£7,996	£7,043	£25,095
5	£3,574	£3,167	£12,264
6	£2,913	£2,588	£10,351
7	£2,304	£2,055	£8,591
8	-£1,267*	-£1,071**	-£1,701***
9	-£1,492*	-£1,269**	-£2,349***
10	-£1,707*	-£1,456**	-£2,965***
11	-£1,910*	-£1,634**	-£3,549***
12	-£2,103*	-£1,803**	-£4,104***
13	-£2,287*	-£1,964**	-£4,632***
14	-£2,461*	-£2,116**	-£5,133***
15	-£5,787*	-£5,024**	-£14,658***

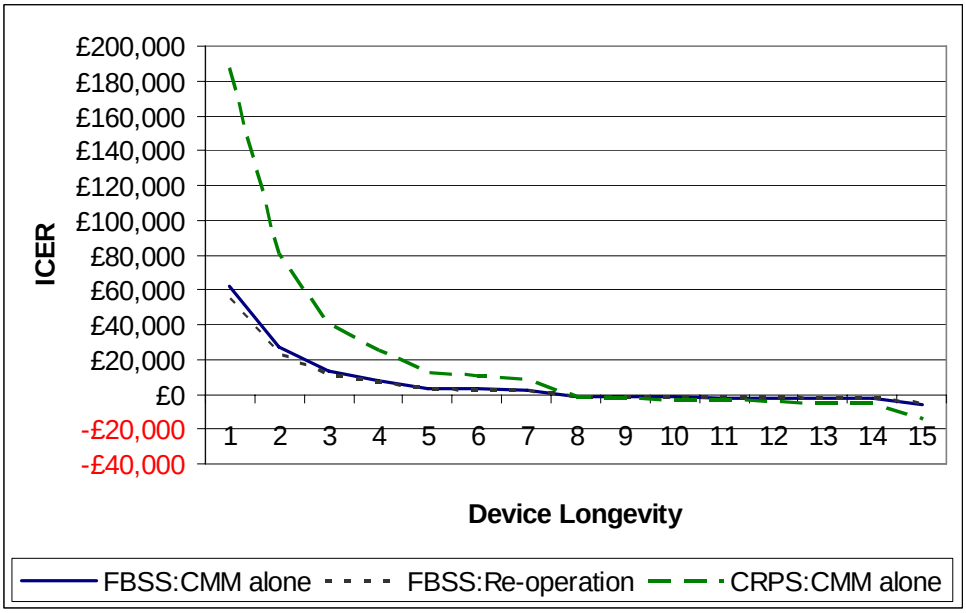
* SCS+CMM dominates CMM alone
** SCS+CMM dominates Re-operation
*** SCS+CMM dominates CMM alone

Receiving a re-implant has an extra cost associated and therefore ICERs are sensitive to it. Kumar *et al.* suggested that the battery's life span of the pulse generator needed replacement after 3.5 to 4.5 years.[110] ABHI's model assumed that the pulse generator needs to be replaced once every 4 years. The Physician Implant Manual by 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 33, 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 re-operation) and CRPS.

From figure 7, it can be seen that for FBSS (CMM alone and re-operation) with a device longevity of 1 years the ICERs are above £30,000, for a device longevity of 2 years the ICERs are below £30,000 whilst 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 whilst 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 33).

Figure 7: Incremental cost effectiveness ratios vs device longevity



Results for 15 year time horizon and 4 year device longevity

Table 34 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 £7,043 per QALY for FBSS (SCS+CMM vs Re-operation) to £25,095 per QALY for CRPS (SCS+CMM vs CMM).

Table 34: 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	£83,775	£10,035
Discounted QALYs	5.66	4.34	1.26
ICER			£7,996
FBSS: SCS+CMM vs Re-operation	**SCS + CMM**	**Re-operation**	**Difference**
Total discounted costs	£87,674	£78,244	£9,430
Discounted QALYs	7.41	5.99	1.34
ICER			£7,043
CRPS: SCS+CMM vs CMM	**SCS + CMM**	**CMM**	**Difference**
Total discounted costs	£86,280	£77,505	£8,775
Discounted QALYs	7.71	7.36	0.35
ICER			£25,095

The results presented in Table 34 suggest that SCS is expected to be more effective for FBSS than for CRPS. This analysis suggest 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).

Another parameter that can impact the results is the cost of the SCS device. Table 35 shows the ICERs for FBSS (SCS+CMM vs CMM) using a 4 year device longevity and a device costs range from £7,000 to £14,000.

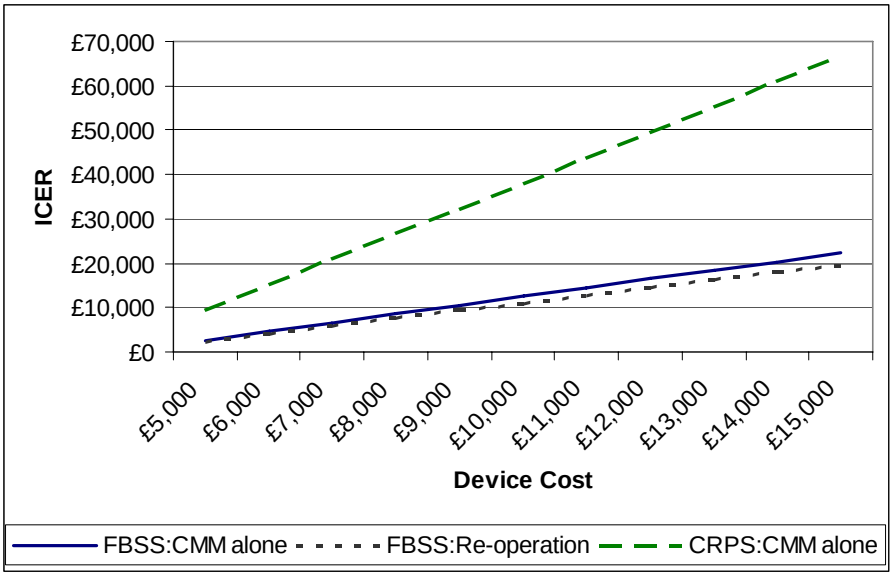
Table 35: Impact of device average price on incremental cost effectiveness ratios

	ICER (£/QALY)		
Device Cost	**FBSS:SCS+CMM vs CMM**	**FBSS:SCS+CMM vs Re-operation**	**CRPS:SCS+CMM vs CMM**
£5,000	£2,563	£2,283	£9,374
£6,000	£4,542	£4,017	£15,101
£7,000	£6,521	£5,751	£20,828
£8,000	£8,500	£7,485	£26,555
£9,000	£10,480	£9,219	£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

At any device cost in the range from £5,000 to £14,000 and device longevity of 4 years, the ICERs for the FBSS indications (CMM and re-operation) are below £20,000 per QALY. In the CRPS indication, when the device cost is £8,000 the ICER is £26,555. When the device cost ranges from £9,000 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 £8,000.

Figure 8: Incremental cost effectiveness ratios vs device cost



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

The most sensitive parameters are device longevity and device cost. Table 36 presents the results when both parameters device longevity and device average price are varied simultaneously, for the FBSS indication (SCS+CMM vs CMM). The tables for FBSS (SCS+CMM vs Re-operation) and CRPS are presented in Appendix 11.

Table 36: 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	£6,326	£8,796	£11,265	£13,735	£16,205	£18,674	£21,144	£23,614	£26,083	£28,553	£31,023
4	£2,563	£4,542	£6,521	£8,500	£10,480	£12,459	£14,438	£16,418	£18,397	£20,376	£22,356
5	-£694	£861	£2,416	£3,971	£5,526	£7,081	£8,636	£10,191	£11,746	£13,301	£14,856
6	-£1,181	£311	£1,802	£3,294	£4,785	£6,277	£7,768	£9,260	£10,751	£12,243	£13,734
7	-£1,630	-£197	£1,236	£2,669	£4,103	£5,536	£6,969	£8,402	£9,835	£11,268	£12,701
8	-£4,260	-£3,170	-£2,079	-£989	£101	£1,192	£2,282	£3,372	£4,463	£5,553	£6,643
9	-£4,426	-£3,357	-£2,289	-£1,220	-£151	£918	£1,986	£3,055	£4,124	£5,192	£6,261
10	-£4,584	-£3,536	-£2,487	-£1,439	-£391	£657	£1,705	£2,753	£3,802	£4,850	£5,898
11	-£4,734	-£3,705	-£2,676	-£1,648	-£619	£410	£1,438	£2,467	£3,496	£4,524	£5,553
12	-£4,876	-£3,866	-£2,856	-£1,846	-£836	£174	£1,185	£2,195	£3,205	£4,215	£5,225
13	-£5,011	-£4,019	-£3,026	-£2,034	-£1,041	-£49	£944	£1,936	£2,928	£3,921	£4,913
14	-£5,140	-£4,164	-£3,188	-£2,213	-£1,237	-£261	£715	£1,690	£2,666	£3,642	£4,617

ICERs are below or very close to £30,000 per QALY for any device price from £7,000 to £15,000 when the device longevity is 3 years. The ICER is below £20,000 per QALY for a device cost between £7,000 and £15,000 if the device longevity is 4 years or more. Appendix 11 presents the ICERs for FBSS (SCS+CMM vs re-operation) and CRPS.

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 10). Monte Carlo sampling techniques (10,000 samples) were used to generate information on the probability that each indication (FBSS: SCS vs CMM, FBSS: SCS vs Re-operation, and CRPS: SCS vs 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 37 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 £[redacted] and a 15 year time horizon). The 95% confidence interval indicates the uncertainty around the mean benefit.

Table 37: Impact of device average price and device longevity on ICER

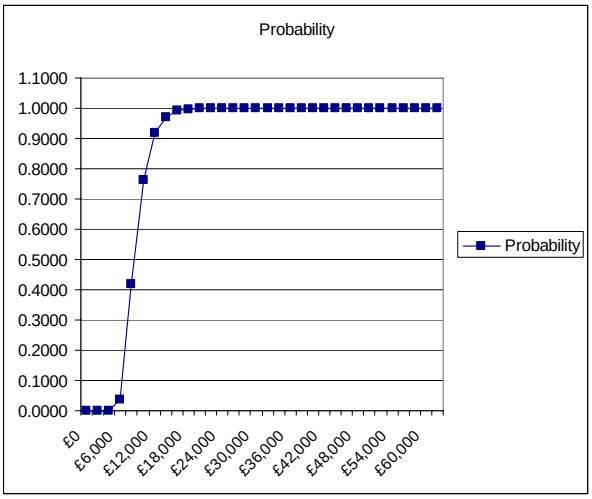
£20,000	**Standard Deviation Net Benefit**	**Mean Net Benefit**	**95% C.I. for Mean Net Benefit**		**Distribution (95% C.I.) for Net Benefit**	
FBSS: SCS+CMM vs CMM alone	5,797	£13,989	£13,875	£14,103	£3,688	£25,955
FBSS: SCS+CMM vs re-operation	5,322	£15,539	£15,435	£15,643	£6,193	£26,331
CRPS: SCS+CMM vs CMM alone	2,619	£1,732	£1,681	£1,783	-£3,178	£6,924
£30,000	**Standard Deviation Net Benefit**	**Mean Net Benefit**	**95% C.I. for Mean Net Benefit**		**Distribution (95% C.I.) for Net Benefit**	
FBSS: SCS+CMM vs CMM alone	8,939	£25,931	£25,756	£26,106	£10,150	£44,467
FBSS: SCS+CMM vs re-operation	8,399	£27,756	£27,591	£27,921	£12,980	£44,710
CRPS: SCS+CMM vs CMM alone	4,094	£6,931	£6,851	£7,011	-£678	£15,003

FBSS: SCS+CMM vs 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 £[redacted] 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 99.86%. Additionally, at a £30,000 per QALY threshold this probability is around 99.99%.

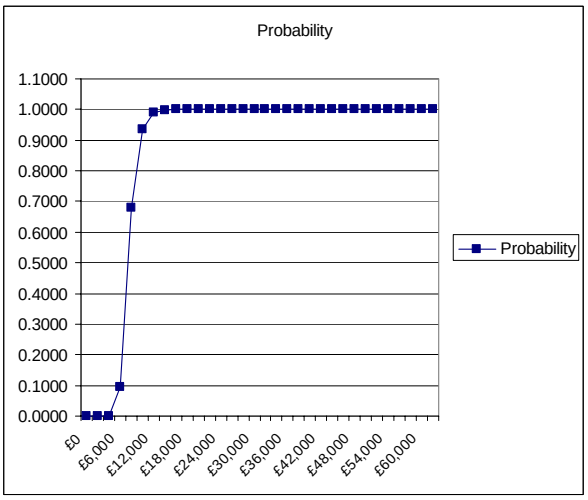
Figure 9: Cost effectiveness acceptability curve for FBSS: SCS+CMM vs CMM



FBSS: SCS+CMM vs re-operation

The results found in the probabilistic analysis using the base case, suggest that SCS+CMM compared to re-operation 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%.

Figure 10: Cost effectiveness acceptability curve for FBSS: SCS+CMM vs Re-operation

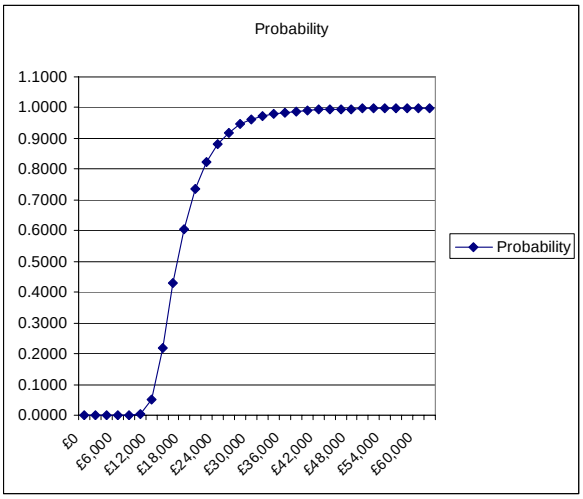


CRPS: SCS+CMM vs CMM alone

The results of the probabilistic analysis, using a 15-year horizon, a 4 year device longevity and a device price of £[redacted], suggest that the probability of SCS+CMM being cost effective

at a £20,000 per QALY threshold is around than 77% (figure 11). Additionally, at a £30,000 per QALY threshold this probability is around 96%.

Figure 11: Cost effectiveness acceptability curve for CRPS: SCS+CMM vs CMM



6.3.3.1 Ischaemic pain model results

This section reports the results of the cost effectiveness analysis of SCS in the treatment of refractory angina. Due to the lack of evidence to demonstrate whether SCS improves the overall survival as compared to revascularisation (CABG or PCI) or medical treatment, the results are presented as a threshold analysis. This analysis presents the necessary improvement that patients receiving a SCS implant would have to demonstrate in order 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: 1) patients clinically appropriate to receive CABG, 2) patients clinically appropriate to receive PCI and 3) patients clinically appropriate to receive both revascularisation procedures.

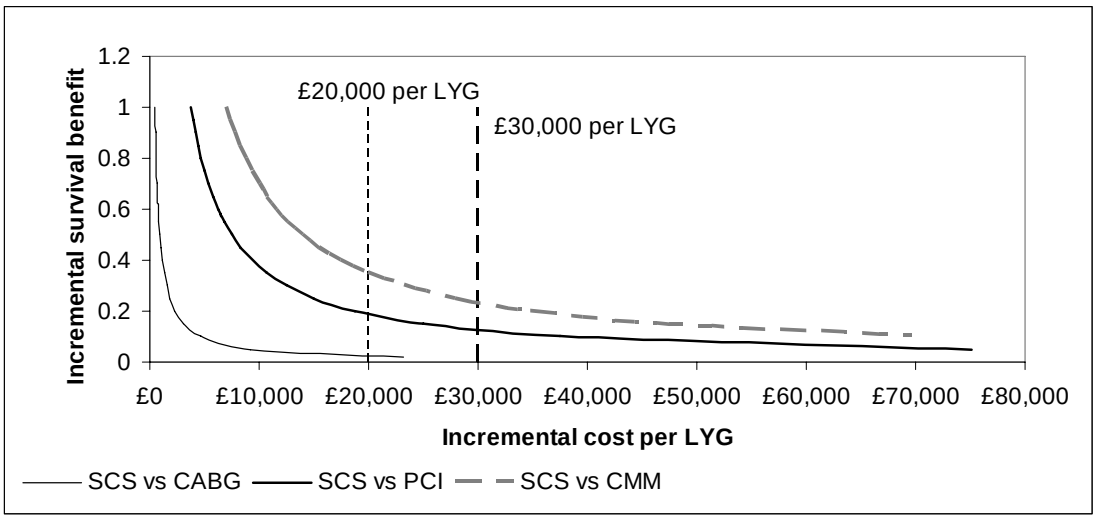
Scenario 1: Patients clinically appropriate to receive CABG

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 to 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 to 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 to CMM in order to achieve incremental costs per LYG below £20,000. Figure 12 shows that SCS+CMM should provide an additional 0.23 to achieve an incremental cost per LYG of £30,000.

Figure 12 Threshold analysis in terms of incremental cost per LYG



Figures 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 incremental cost effectiveness ratios (ICERs).

Figure 13 Threshold analysis in terms of incremental cost per QALYs

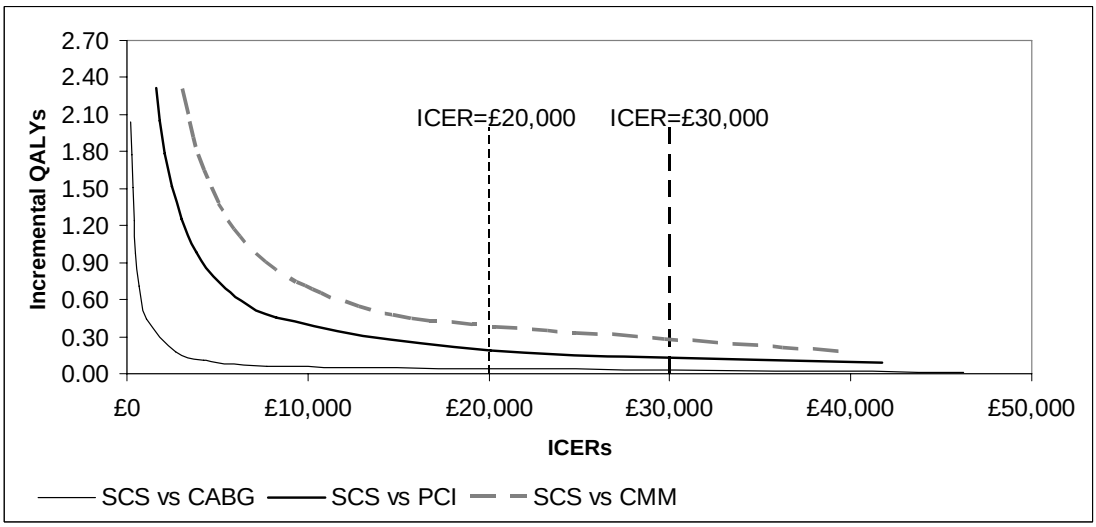


Table 38 shows that for patients who are clinically appropriate to receive CABG, SCS+CMM must provide at least an additional 0.0231 and 0.0154 QALYs when compared to CABG to achieve ICERs of £20,000 and £30,000 per QALY gained, respectively. Therefore, the SCS utility value to achieve an ICER of £20,000 per QALY is 0.6218 whilst the utility value should be 0.6203 in order 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 whilst the utility value is 0.5884 in order to achieve £30,000 per QALY gained. Table 38 also shows that SCS + CMM must provide at least an additional 0.3480 and 0.2320 QALYs when compared to 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 whilst the utility value is 0.6103 to achieve £30,000 per QALY gained.

Table 38 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

Scenario 2: Patients clinically appropriate to receive PCI

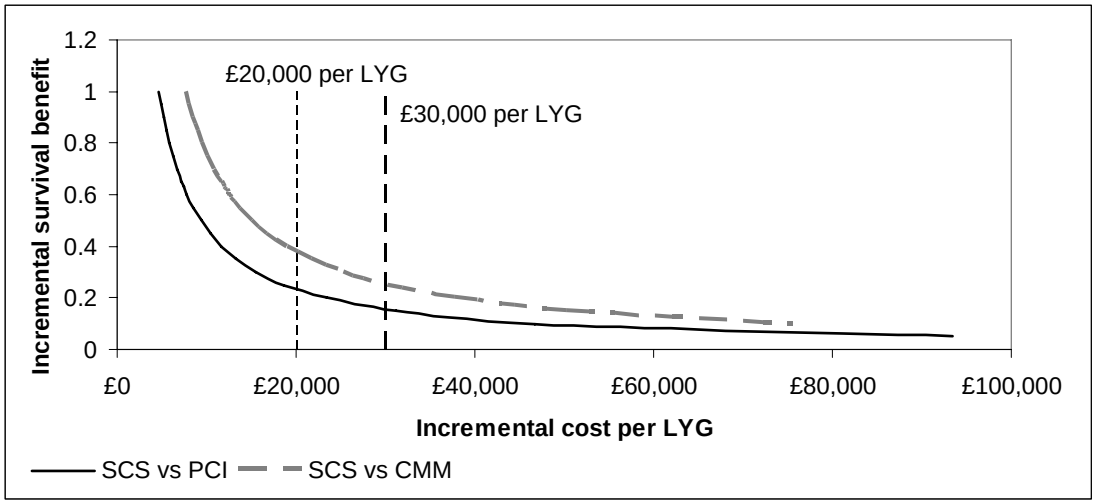
For patients who are clinically appropriate to receive PCI, SCS+CMM dominates in terms of cost per LYG when compared with CABG. This means that SCS cost less and accrued more survival benefits. The model suggests that in terms of incremental cost effectiveness ratios (£/QALY), SCS+CMM is dominant when the incremental QALYs are in a 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 to 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 to CMM in order 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 14 Threshold analysis in terms of incremental cost per LYG



Figures 15 presents the incremental cost effectiveness ratios of SCS + CMM compared with 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 incremental cost effectiveness ratios (ICERs).

Figure 15 Threshold analysis in terms of incremental cost per QALYs

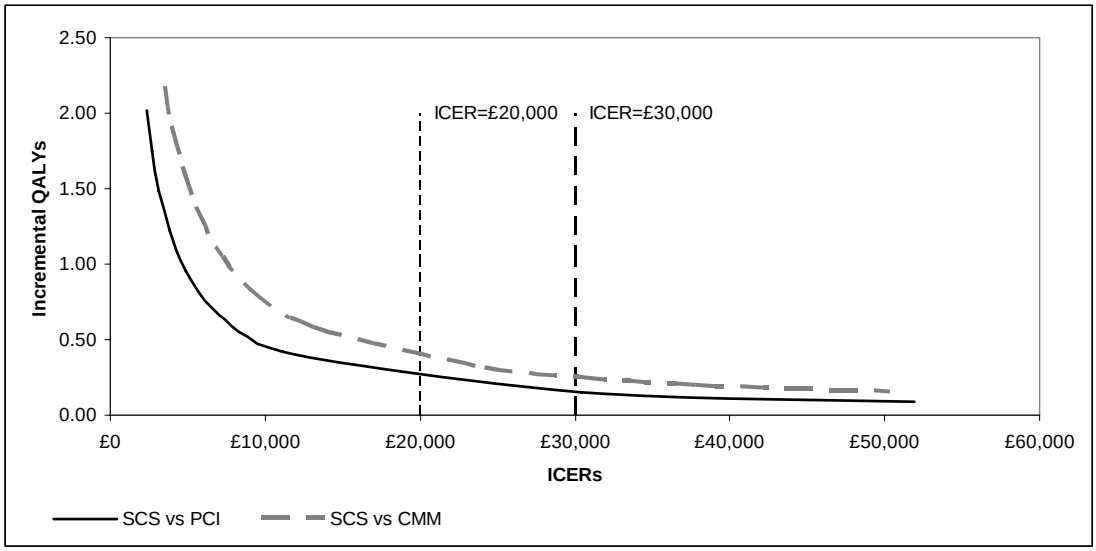


Table 39 shows that for patients who are clinically appropriate to receive PCI, SCS+CMM must provide at least an additional 0.2337 and 0.1558 QALYs when compared to PCI to

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 0.6650 whilst the utility value is 0.6504 in order 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, respectively. The SCS utility value to achieve an ICER of £20,000 per QALY is 0.6620 whilst the utility value is 0.6384 to achieve £30,000 per QALY gained.

Table 39 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

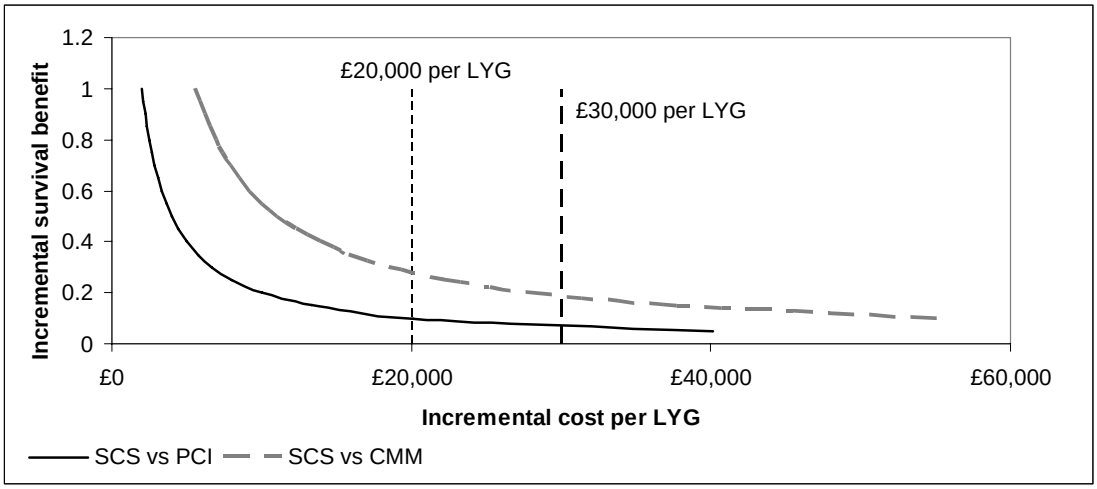
Scenario 3: Patients clinically appropriate to receive both revascularisation procedures

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 to 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 to CMM in order 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 16 Threshold analysis in terms of incremental cost per LYG



Figures 17 presents the incremental cost effectiveness ratios of SCS + CMM compared with 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 incremental cost effectiveness ratios (ICERs).

Figure 17 Threshold analysis in terms of incremental cost per QALYs

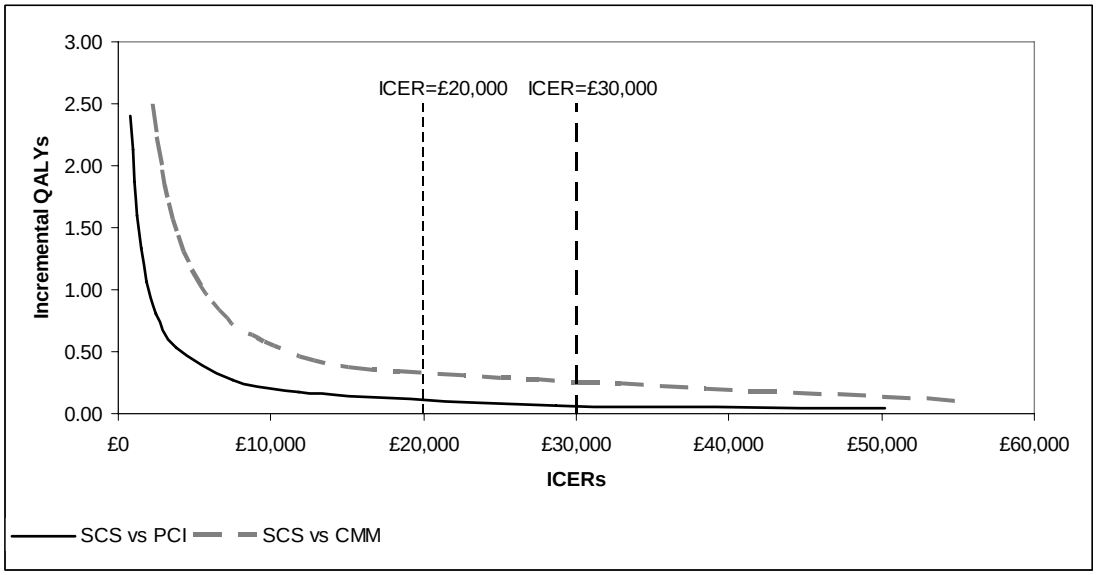


Table 40 shows that for patients who are clinically appropriate to receive CABG and PCI, SCS+CMM must provide at least an additional 0.1004 and 0.0669 QALYs when compared to PCI to achieve ICERs of £20,000 and £30,000 per QALY gained, respectively. Therefore, the SCS utility value to achieve an ICER of £20,000 per QALY is 0.5687 whilst the utility value is 0.5624 in order to achieve £30,000 per QALY gained. SCS+CMM must provide at least an additional 0.2762 and 0.1842 QALYs when compared to 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 whilst the utility value is 0.5657 to achieve £30,000 per QALY gained.

Table 40 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

6.3.4 Discussion of results

6.3.4.1 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 £[redacted], suggest that the cost effectiveness estimates for SCS intervention in patients with FBSS who have 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 to CMM alone and re-operation) are below a threshold of £20,000 per QALY gained. In CRPS (compared to 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 £5,000 to £15,000, the ICERs range from £2,563 per QALY to £22,356 per QALY for patients with FBSS when compared to CMM alone and from £2,283 per QALY to £19,624 per QALY for patients with FBSS when compared to re-operation. For patients with CRPS the ICERs range from £9,374 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 £6,000 and £8,000 to reain under £30,000 per QALY.

If the device longevity (1 to 14 years) and the device average price (£5,000 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.

Table 41 shows a comparison between the results obtained by ABHI and ScHARR models. In both FBSS indications (CMM alone and re-operation), the main differences appear to be in the costs. This is due to ABHI using estimated costs obtained from the PROCESS trial (in academic confidence) and ScHARR using estimated costs obtained from other sources as outlined in Section 6.3. In CRPS the main differences appear to be in both parameters costs and QALYs. This is due to the different estimated costs used in the models and the difference in the utility values input in each model as outlined in Section 6.3.

Table 41 Results comparison between ABHI and ScHARR model

	ABHI model			ScHARR model		
50% pain threshold criteria	Cost Difference	QALYs Difference	ICER	Cost Difference	QALYs Difference	ICER
FBSS: SCS+CMM vs CMM alone						
Device Longevity						
Basecase: 4-year	£11,439	1.25	£9,155	£10,035	1.26	£7,996
2-year			£30,285			£26,755
7-year			£2,745			£2,304
> 7 years			SCS+CMM dominates			SCS+CMM dominates
FBSS: SCS+CMM vs re-operation						
Device Longevity						
Basecase: 4-year	£10,651	1.34	£7,954	£9,430	1.34	£7,043
2-year			£26,445			£23,536
7-year			£2,362			£2,055
> 7 years			SCS+CMM dominates			SCS+CMM dominates
CRPS: SCS+CMM vs CMM alone						
Device Longevity						
Basecase: 4-year	£12,041	0.64	£18,881	£8,775	0.35	£25,095
2-year			£52,541			£80,388
7-year			£8,737			£8,591
> 7 years			SCS+CMM dominates			SCS+CMM dominates

6.3.4.2 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 SCS dominates (cost less and accrued more survival benefits) CABG.

The threshold analysis suggests that for patients clinically appropriate for CABG in order 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) in order to achieve £20,000 and £30,000 per LYG.

For patients appropriate for CABG, in order 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 to PCI and at least 0.6321 when compared to CMM. For ICERs of £30,000 QALY gained or less, the expected utility value must be at least 0.6203 when compared to CABG, at least 0.5884 when compared to PCI and at least 0.6103 when compared to 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 to CMM. For ICERs of £30,000 QALY gained or less, the expected utility value must be at least 0.5624 when compared to PCI, at least 0.5657 when compared to CMM.

It should be restated that due to 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.

6.4 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 of

639 patients received a SCS implant in England in 2006.[54] It is assumed that the same number received an implant in year 2007. Table 42 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 (personal communication).

Table 42 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

The estimated budget impact for SCS treatment of FBSS, CRPS and refractory angina is presented in Table 43.

Table 43 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

The reduction in costs in FBSS from year 1 to year 2 is due to cost savings of those patients that had an implant at year 1 (£1,622 of cost savings). Nevertheless, year 2 also considers those patients receiving a first time SCS implant. This pattern is repeated until year 4. The costs increase at year 5 is due to 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.

7. 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 may require giving up work, or a job change or change of job responsibility.[123] Inability to work impacts society by payment of disability benefits.

Patients with cognitive impairment may be considered incapable of operating an SCS device. According to BPS, 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 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 HRQoL have been validated translated into languages other than English which could be relevant to patients without English as a first language.[125,29,126,30,127]

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

8. DISCUSSION

8.1 Statement of principle findings

Clinical effectiveness data were available from 11 randomised controlled trials, 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 ITT analysis), adequately powered trials were available for neuropathic conditions FBSS and complex regional pain syndrome (CRPS) type I. Trial evidence reported that SCS was significantly more effective than conventional medical management (CMM) in reducing neuropathic pain of failed back surgery syndrome or CRPS. 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 use of analgesics up to 6 months, not at 18 months, but no other measures differed significantly between groups, although there was a nonsignificant trend for a subgroup of patients with intermediate skin microcirculation prior to treatment to favour SCS for amputation rate. Other CLI trials found 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 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 SCS was more effective than no SCS or an inactive device in delaying angina pain onset during exercise or 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 re-operation) is a cost effective intervention. In the CRPS indication the ICERs obtained tend to be higher, and in some cases above £30k per QALY. This is due 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 NHS patients. Further research is required to allow more precise estimates to be calculated in the analysis of CRPS clinical effectiveness.

8.2 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 included trials of relevance to UK practice. 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 to CMM or re-operation 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 including studies which have not been published in English would have altered the results. A number of conservative assumptions were taken. Some assumptions were made with respect to the clinical effectiveness of SCS in patients with CRPS type I, due to the data obtained in the RCT. It was also assumed that there were no complications associated to 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 not significant difference between groups in terms of pain relief, for SCS versus CMM or analgesic treatment.

8.3 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 of 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 influence 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 due to device withdrawal and not to a parameter defined as tolerance (gradual loss of pain control even when the system is fully functional). There is as yet no evidence to support the etiology of this phenomenon as may be related to plasticity of central pain processing systems.

9. CONCLUSIONS

9.1 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.

Conclusions on the cost effectiveness of SCS in treatment of neuropathic pain

This analysis suggests that in patients with FBSS who have 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 £7,996 (£5,845-£14,215) compared to 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 £7,043 (£5,562-£11,006) compared to re-operation. SCS+CMM is expected to dominate re-operation 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-£32,814) compared to 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 CABG in patients clinically appropriate to receive PCI and in patients clinically appropriate to receive CABG and PCI.

The threshold analysis suggests that for patients clinically appropriate for CABG in order 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.

Although, it is difficult to determine whether SCS intervention represents value for money, the threshold analysis suggests that the ICER 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.

9.2 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 CLI subgroups (intermediate skin microcirculation, adequate TcpO2, 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, with a notable lack in the case of angina. There is no good way to blind patients in SCS trials. Sham stimulation doesn't work because patients are aware of paraesthesia, although excluding patients with prior use of 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 HRQoL and pain measures is to be recommended. Trials using exercise training to assess outcomes may be more valid with SCS switched on during measurement.

Some forms of chronic pain have low prevalence rates (such as some nerve disorders) making recruitment to RCTs difficult. Multi-centre collaboration may enable adequate samples for RCTS, or other forms of data collection may be necessary. BPS recommend 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 (Personal communication, clinical advisors). 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.

10. APPENDICES

Appendix 1 CE marked indications

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

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

SCS devices with radio-frequency 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 prior to permanent implant.[128]

Appendix 2: Medline search strategy

Strategy below was combined with RCT, 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. 64 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. 66 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. 12 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$).tw.
14. quality adjusted life years/
15. (qaly or qaly$).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. 21 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$.tw.
32. peripheral vascular disease/
33. refactory angina.tw.
34. exp Brachial Plexus Neuropathies/
35. exp Radiation Injuries/
36. post-radiation.tw.
37. exp Amputation/
38. spinal surgery.tw.
39. intercostal$ neuralgia.tw.
40. exp Spinal Cord Injuries/
41. nerve lesion$.tw.
42. nerve dysfunction.tw.
43. nerve damage.tw.
44. nerve patholog$.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. 19 or 20 or 23
83. or/24-81
84. 82 or 83
85. or/1-18
86. 84 and 85

Appendix 3 Quality assessment of included trials

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

Quality assessment of FBSS trials

Trial	**PROCESS**[59,60,61]	**North**[62,63,64]
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 2 or 4) 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

Trial	**PROCESS**[59,60,61]	**North**[62,63,64]
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

Quality assessment of CRPS trial

Trial	**Kemler**[65,66,67]
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

Quality assessment of CLI trials

Trial	**ESES[68,69,70,71,72] (PILOT[58])**	**Suy[73]**	**Jivegard[74]**	**Claeys[75,76,77,78]**
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

Trial	**ESES[68,69,70,71,72] (PILOT[58])**	**Suy[73]**	**Jivegard[74]**	**Claeys[75,76,77,78]**
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

Quality assessment of Angina trials

Trial	**deJongste** [79]	**ESBY**[80,81,82]	**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 LVEF
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*	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	Yes	Mostly. Achieved for variables

Trial	deJongste [79]	ESBY[80,81,82]	SPiRiT[83]	Hautvast[84]
		variables apart from renal disease and smoking		apart from number of myocardial infarctions, and number of coronary angioplasties
Was an intention to treat analysis included?	Yes*	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*	Yes	Yes	Yes

*Paper by DeJongste,[129] apparently describing preliminary results of same study, has more patients (n=24) randomised than reported in 1994 paper

Appendix 4 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 Eddicks, S., Maier-Hauff, K., Schenk, M., Muller, A., Baumann, G., and 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; 93 585-590.	Angina	SCS (4 groups with different stimulation regimens, 1 of which low voltage considered the control treatment) (n=12)	(Same patients - crossovers to other study groups)	16 weeks (4weeks in each of 4 different study regimens)
All patients in the trial had previously had SCS (mean 39months). Crossover study	DiPede Di, Pede F. Long-term effects of spinal cord stimulation on myocardial ischemia and heart rate variability: results of a 48-	Angina	SCS turned on for 24hrs (n=15)	(Same patients - SCS turned off for 24hrs)	48hours

Reason for exclusion	Trial	Indication	Intervention (and sample size)	Comparator (and sample size)	Study period
	hour ambulatory electrocardiographic monitoring. Italian heart journal : official journal of the Italian Federation of Cardiology 2001; 2 690-695.				
Study of withholding stimulation, No data comparing SCS on with SCS off (instead looks into the possibility of clinical rebound after witholding neurostimulation). All patients in the trial had previously had SCS (mean 42 or 34 months for treatment or control group respectively)	Jessurun Jessurun, G. A., DeJongste, M. J., Hautvast, R. W., Tio, R. A., Brouwer, J., van, Lelieveld S., and Crijns, H. J. 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 & Clinical Electrophysiology 1999;	Angina	SCS turned on for 4weeks then off for 4weeks (n=12)	SCS turned off for 4weeks (n=12)	4 weeks control, 8 weeks intervention group

Reason for exclusion	Trial	Indication	Intervention (and sample size)	Comparator (and sample size)	Study period
	22 1432-1439				
All patients in the trial had previously had SCS (and had an unsatisfactory response to SCS). Not randomised	Lind Lind, Goran, Schechtmann, Gaston, Winter, Jaleh, Meyerson, Bjorn A., and Linderoth, Bengt Baclofen-enhanced spinal cord stimulation and intrathecal baclofen alone for neuropathic pain:: Long-term outcome of a pilot study European Journal of Pain, 12 (1), p.132-136, Jan 2008	Neuropathic pain	SCS and baclofen (n=5)	Intrathecal baclofen (n=4)	mean 67months
Not randomised	Amman[100] 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-	Critical limb ischaemia	SCS (2 groups: TcpO2<30mmHg, increased from <10 to >20mmHG, and adequate pain relief and paraesthesia coverage (n=41); others (n=32)	No SCS (n=39)	12 months

Reason for exclusion	Trial	Indication	Intervention (and sample size)	Comparator (and sample size)	Study period
	EPOS). European Journal of Vascular & Endovascular Surgery 2003; 26 280-286.				
Not RCT (test stimulation of 4 days duration with random cross-over design applying to this test phase only, then study is a case series)	Tesfaye Tesfaye, S., Watt, J., Benbow, S. J., Pang, K. A., Miles, J., and MacFarlane, I. A. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet 21-12-1996; 348 1698-1701	Diabetic peripheral neuropathy	SCS. Test stimulation placebo then active stimulator (n=5)	SCS. Test stimulation active stimulator then placebo (n=5)	2days then cross-over 2days
No usable outcome data, not all patients had angina, no mention of pain duration	Fiume Fiume, D. Permanent spinal cord stimulation in patients with coronary heart disease. Preliminary data. Acta Neurochir Wien 1994; 129 243-244	Coronary heart disease (most with angina)	SCS (n=13)	No SCS (n=6)	mean follow-up 4to5months

Appendix 5 Included studies in this report versus industry submission

The same RCTs for neuropathic pain are included in this report and the industry submission.

In the industry submission Appendix 4, references Spincemaille, Klomp and Ubbink are listed as 3 trials, but are all publications from the ESES trial. This report includes the 3 RCTs from the industry submission (ESES, Jivegard, Claeys) and in addition includes the Suy RCT.
In the industry submission Appendix 5, 7 angina studies are listed, but only outcomes for 6 of these trials, as 1 trial (Jessurun) does not report any relevant data; this trial is excluded from this report (see Appendix X Excluded studies). This report also excludes 2 crossover studies for which the populations had been exposed to SCS prior to study (Eddicks and Di Pede) (see Appendix X Excluded studies). The 4 RCTs included in ScHARR-TAG's report are also listed in the industry submission (DeJongste, ESBY, SPiRiT, Hautvast).

Appendix 6 Data extraction tables

Appendix 6.1 Data extraction FBSS

FBSS Trial details

Trial name	**PROCESS**[59]
Publication type of main reference	Kumar (2007) Full report in peer-reviewed journal[59]
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, ODI, 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, Inc., Minneapolis), 3 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

Trial name	PROCESS[59]
	therapy (e.g. spinal surgery, intrathecal drug delivery)

Trial name	North[62]
Publication type of main reference	North (2005) Full report in peer-reviewed journal[62]
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 Inc. Minneapolis, MN) 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 Inc).
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.

Trial name	North[62]
	Plus CMM: standard postoperative analgesics, preoperative analgesics (tapered as rapidly as possible); physical therapy in accordance with the post-spinal surgery physical therapy protocol of the institution

FBSS trial participants

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	Test stimulation n=52 – 9 failed, but 5 of these requested and received permanent implant. Permanent implant n=48 By 6 month follow-up, 2 of these withdrew consent (treatment ended) (n=46), by 12 month follow-up n=45
Number receiving treatment according to allocation: control	Started treatment n=48. By 6 month follow-up, 4 withdrew consent (n=44), by 12 month follow-up (28 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 to 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, exam of sensory/motor/reflex change, with supporting tests e.g. X-ray, MRI and EMG); Pain duration at least 6 months (after a minimum of one anatomically successful surgery for a herniated disc); Prior therapy at least 1 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.

Trial name	**PROCESS**[59]
Characteristics of participants at baseline - intervention group: age	mean 48.9 (SD 10)
Characteristics of participants at baseline - control group: age	mean 52.0 (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)
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) ;

Trial name	**PROCESS**[59]
	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)

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	Test stimulation n=24 (6 couldn't get authorisation from insurance company/stroke), 7 failed test stimulation, of these 5 crossed over to reoperation, 2 lost to follow-up Permanent implant n=17
Number receiving treatment according to allocation: control	Started treatment n=26 (4 couldn't 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; Prior therapy one or more lumbosacral spine surgeries.

Trial name	**North**[62]
	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, 30 female, 30 male

FBSS trial results

Trial name	**PROCESS**[59]
Pain outcome - VAS (details)	Patient self-completed questionnaires, VAS 0-100mm, three times per day separately for back and leg pain during four 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 categorized 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 5 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%). Odds Ratio 9.23 (99%CI 1.99-42.84). P<0.001 (excluding 5 patients who failed SCS test stimulation p<0.001). At 6 months ITT "worst-case" analysis p=0.002. (subgroup analysis patients with either less 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 nonsignificant (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 <

Trial name	PROCESS[59]
	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 to 71%), OR 8.73 (99%CI 2.46 to 31.01) p<0.001 Agree with treatment between group risk difference (99%CI) 36% (13 to 59%), OR 6.14 (99%CI 1.66 to 22.67) <0.001
Medication use outcome - details	Use of pain medication, number of patients taking any medication, 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.
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; NSAIDs 17 (34%) p=0.58; Antidepressants 17 (34%) p=0.63; Anticonvulsants 13 (26%) p=0.18

Trial name	**PROCESS**[59]
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; NSAIDs -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).
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

Trial name	**PROCESS**[59]
physical and functional abilities results ODI : comparison	At 6 months, between group risk difference -11.2 (99%CI -21.2to -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
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):	N=32, 4 of whom failed test stimulation (n=28 received SCS)

Trial name	**PROCESS**[59]
control group	
health-related quality of life SF36 details	Short-Form 36 (SF-36) questionnaire to assess quality of life
health-related quality of life results SF36: intervention group	Short-Form 36 – change from baseline mean (SD): 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	Short-Form 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
health-related quality of life results	At 6 months ITT analysis Short-Form 36 – difference in means (99%CI)

Trial name	PROCESS[59]
SF36: comparison	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	84 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%) surgery required 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, IPG migration 1, Loss of therapeutic effect, loss of paraesthesia, or unpleasant paraesthesia 6, Techniquea 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 event 18 (35%). Patients with 1 or more drug adverse event 2 (4%); Drug adverse events 2; Patients with 1 or more event of extra pain 0 (0%); Events of extra pain 0; Patients with 1 or more new illness/injury/condition 13 (25%); Events of new illness/injury/condition 16;

Trial name	**PROCESS**[59]
	Patients with 1 or more worsening of preexisting 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 1 or more drug adverse event 10 (21%); Drug adverse events 12 ; Patients with 1 or more event of extra pain 2 (4%) ; Events of extra pain 2 ; Patients with 1 or more new illness/injury/condition 11 (23%) ; Events of new illness/injury/condition 13 ; Patients with 1 or more worsening of preexisting condition 7 (15%) ; Events of worsening of pre-existing condition 10
Deaths during follow-up period	0 (at 12 months)

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	Achieving "success" n=3 of 26 (12%)

Trial name	**North**[62]
satisfaction: control group	
pain results pain relief/patient satisfaction : comparison between groups	Follow-up mean 2.9 years, SCS sig 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	nonsig 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 sig 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	nonsig between groups
Physical and functional abilities outcome work status (details)	Patient self-reported employment status

Trial name	**North**[62]
physical and functional abilities results work status: comparison	nonsig between groups. At baseline 52% retired/perm disabled. Study end - 1 dropped out from employment, one increased from part-time to full-time employment
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 didn't 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	1 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	1 patient died of cardiac event just before 6 month follow-up test - SCS group (allocated and received SCS treatment)

Appendix 6.2 Data extraction CRPS type I

CRPS type I Trial details

Trial name	**Kemler**[65]
Publication type of main ref (ie full report or abstract)	Kemler 2000[65] Full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, 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 percent to detect 2.3cm 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	Visual analogue scale (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).

Trial name	**Kemler**[65]
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 two days between sessions. Intensity reduced if pain during exercise had not returned to the pre-exercise level within 24 hours. Physical therapy total duration six months, starting after the second assessment, continuation after 6 months was optional. To ensure standardisation, physical therapists were trained.

CRPS 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 0-10cm, 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 3 of the following: oedema; increased nail growth; increased hair growth; hyperhidrosis; abnormal skin colour; hypoesthesia; 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 (six months of physical therapy, sympathetic blockade, transcutaneous electrical nerve stimulation, and pain medication); aged 18-65. Exclusion criteria: Raynaud's disease, current or previous neurologic 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.

Trial name	**Kemler**[65]
Characteristics of participants at baseline - intervention group: age	mean 40 (SD 12)
Characteristics of participants at baseline - control group: age	mean 35 (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 0-10cm mean 7.1cm (SD 1.5). HRQoL VAS 0-100 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 90-item Symptom Check List (SCL-90, a scale of 90-450 with higher score indicating greater psychological distress) mean 146 (SD 32). Pain score on VAS 0-10cm mean 6.7cm (SD 1.2). HRQoL VAS 0-100 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.

CRPS type I trial results

Trial name	**Kemler[65]**
Pain outcome - VAS (details)	Intensity of pain assessed on a visual-analogue scale (VAS) from 0cm (no pain) to 10cm (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 2.1cm (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 -1.6cm, at 4 years -1.7cm)[66] Per treatment analysis at 6 months decreased by a mean of 3.6 cm (P<0.001). At 2 years per treatment analysis mean pain reduction 3cm(SD2.7).[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 0cm (SD 1.5).[67] At 5 years (n=13) mean pain intensity reduced from baseline by 1.0 cm (at 3 years -0.7cm, at 4 years -1.0cm)[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). At 2 years per treatment analysis p<0.001.[67]
Pain outcome - McGill (details)	McGill Pain Questionnaire including pain-rating index
	At 6 months Nonsig between groups. Per treatment analyses at 6 months, and at 24 months, 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

Trial name	Kemler[65]
	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 24 months P<0.001.[67]
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 3kg (SD 8); range of motion wrist mean 2degrees (SD 10); range of motion all fingers mean 23degrees (SD 181). Foot - function seconds required to perform task mean -1sec (SD 3); dorsiflexion N 14(28); plantar flexion N 23(63); range of motion ankle mean 11degrees (SD 18). At 2 years, upper extremities Functional score (from n=21), upper extremities: function mean 2sec (SD 14); strength 0kg (SD 5); range of motion wrist 0degrees (30); range of motion hand -18 degrees (181). At 2 years lower extremities functional score (from n=14): function -3 sec (SD4); dorsiflexors N 11 (27); plantarflexors N 14(43); range of motion ankle 0degrees (SD16).[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 1kg (SD 3); range of motion wrist mean -3degrees (SD 30); range of motion all fingers mean -39degrees (SD 190). Foot - function seconds required to perform task

Trial name	**Kemler**[65]
	mean -1sec (SD 3); dorsiflexion N 3(4); plantar flexion N 40(51); range of motion ankle mean 8degrees (SD 10). At 2 years, upper extremities Functional score (from n=10), upper extremities: function mean 4sec (SD 21); strength -1kg (SD 3); range of motion wrist -5degrees (37); range of motion hand -119 degrees (309). At 2 years lower extremities functional score (from n=5): function -5sec (SD5); dorsiflexors N -8 (27); plantarflexors N 20(44); range of motion ankle 13degrees (SD8).[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), upper extremities: function p=0.78; strength p=0.54; range of motion wrist p=0.73; range of motion hand p=0.36. At 2 years lower extremities functional score (from n=5): function p=0.48; dorsiflexors p=0.21; plantarflexors 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 24 months, 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)
Complications and adverse effects	Test stimulation 4 patients dural puncture.

Trial name	**Kemler**[65]
outcomes SCS group	Of n=24 with permanent implant, At 6 months, implantation was complicated by dural puncture in two patients (with headache in one). Six (25 percent) had a total of 11 other complications. Four patients 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 four of the five patients; correct positioning required three procedures in the fifth patient). During 2yr 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 6.3 Data extraction CLI

CLI Trial details

Trial name	**ESES**[68]
Publication type of main ref (ie full report or abstract)	Spincemaille (2000) [68] Full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Multicentre, 17 centres, 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	NHP, 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, Minneapolis, MN, USA), 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.

Trial name	**Suy**[73]
Publication type of main ref (ie full report or abstract)	Suy (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

Trial name	**Jivegard**[74]
Publication type of main ref (ie full report or abstract)	Jivegard (1995) [74] Full report in peer-reviewed journal
Study design	Prospective RCT

Setting	2 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 and rating on 5-point scale, skin temperature VAS 0-100, ABI, STBI, 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 Inc) 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

Trial name	**Claeys[76]**
Publication type of main ref (ie full report or abstract)	Claeys (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	ABI, complications, adverse effects
Intervention (description)	SCS (plus PGE1 and standard wound care)
SCS details (device and implantation)	Test stimulation: quadripolar lead (Pisces Quad 387A, Medtronic) percutaneous, trial period of 1week 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

CLI trial participants

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; thus patients with implant and optimal stimulation n=51)[69]
Number receiving treatment according to allocation: control	60
Inclusion/exclusion criteria	Inclusion: Surgically non-reconstructible atherosclerotic vessel disease 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 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; Presence of a cardiac pacemaker; Inadequate patient compliance due to psychological or social incompetence
Characteristics of participants	mean age 73 (SD 9.8)

Trial name	ESES[68]
at baseline - intervention group: age	
Characteristics of participants at baseline - control group: age	mean age 72 (SD 10.6)
Characteristics of participants at baseline - intervention group: sex	27 female (45%); male 33 (55%)
Characteristics of participants at baseline - control group: sex	23 female (38%); male 37 (62%)
Characteristics of participants at baseline - intervention group: other	Diabetes 37% (n=22); Contralateral leg Symptomatic 32% (n=19), Amputated 15% (n=9); Smoking status Not for > 1 year 37% (n=22), Still smoking 30% (n=18); CVA/TIA 22% (n=13); Myocardial infarction 38% (n=23); Angina pectoris 20% (n=12); ulcerations/gangrene 63% (n=38); Gangrene Dry 40% (n=24), Wet 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-brachial index (mean, SD) 0.23 ± 0.16
Characteristics of participants at baseline - control group:	Diabetes 38% (n=23); Contralateral leg Symptomatic 48% (n=29), Amputated 12% (n=7);

Trial name	ESES[68]
other	Smoking status Not for > 1 year 27% (n=16), Still smoking 44% (n=26); CVA/TIA 27% (n=16); Myocardial infarction 37% (n=22); Angina pectoris 25% (n=15); ulcerations/gangrene 68% (n=41); Gangrene Dry 38% (n=23), Wet 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-brachial index (mean, SD) 0.28 ± 0.13

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	18

Trial name	**Suy**[73]
according to allocation: control	
Inclusion/exclusion criteria	Inclusion: chronic ischaemic rest pain related to peripheral vascular occlusive disease, either due to arteriosclerosis (ASD) or to 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.
Characteristics of participants at baseline - intervention group: age	mean for patients with ASD (n=16) 66, mean for patients with Buerger's (n=4) 36, range for all patients 26-80
Characteristics of participants at baseline - control group: age	mean for patients with ASD 65 (n=11), mean for patients with Buerger's (n=7) 46, range for all patients 36-80
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 I 3; type II 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 I 1; type II 1. Smoking: non-smoker 0; stopped smoking 5; smoker 13.
Characteristics of participants at	30 of 38 patients on narcotic analgesic treatment

Trial name	**Suy**[73]
baseline - group not indicated	

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	22
Number receiving treatment according to allocation: control	26
Inclusion/exclusion criteria	Inclusion: 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 due to poor outflow conditions. All patients had undergone digital subtraction arteriography. Exclusion: rapidly progressing ischaemia, gangrene of more than one toe; extensive infection and/or extensive non-healing ischaemic

Trial name	Jivegard[74]
	ulcerations; poor cooperability; presence of associated diseases prohibiting the use of SCS
Characteristics of participants at baseline - intervention group: age	mean age 73 (SD 12)
Characteristics of participants at baseline - control group: age	mean age 73 (SD 12)
Characteristics of participants at baseline - intervention group: sex	11 female (44%); 14 male (56%)
Characteristics of participants at baseline - control group: sex	12 female (46%); 14 male (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 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%), ASA 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%)

Trial name	**Jivegard**[74]
	Dextropropoxyphen n=11 (42%) Paracetamol n=11 (42%), ASA n=2 (8%)
Characteristics of participants at baseline - group not indicated	

Trial name	**Claeys**[76]
Number randomised (total)	86 (randomisation 7days after start of PGE1 therapy)
Number randomised: intervention group	45
Number randomised: control group	41
Number receiving treatment according to allocation: intervention	45
Number receiving treatment according to allocation: control	41
Inclusion/exclusion criteria	Inclusion: Fontaine stage IV patients with endstage peripheral arterial occlusive disease (PAOD) undergoing 21 day intravenous prostaglandin E1 (PGE1) therapy (80microg/day) for nonhealing 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 nonhealing foot ulcers or dry gangrene, ulcers or gangrene present for a minimum of 3 weeks.

Trial name	**Claeys[76]**
	Exclusion: 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, Buergers' disease, unstable angina, neuropsychiatric diseases.
Characteristics of participants at baseline - intervention group: age	67.7 (SD 11.9)
Characteristics of participants at baseline - control group: age	69.9 (SD 10.2)
Characteristics of participants at baseline - intervention group: sex	female n=19, male n=26
Characteristics of participants at baseline - control group: sex	female n=18, male n=23
Characteristics of participants at baseline - intervention group: other	PAOD n=39; PAOD plus diabetes mellitus n=6; Number of ischaemic lesions 1lesion n=37, 2lesions n=4, 3+lesions n=4; hypertension n=34; cigarette pack years 44.4; ankle pressure on the treated limb 0mmHg n=12, 20mmHg n=12, 40mmHg n=21; ABI 0.287+/-0.19; TcPO2 on the treated foot 10.0mmHg (+/-7.8); walking ability unable to walk n=25, walk less than 50m n=20; mean walking distance 24m
Characteristics of participants at baseline - control group: other	PAOD n=34; PAOD plus diabetes mellitus n=7; Number of ischaemic lesions 1lesion n=29, 2lesions n=9, 3+lesions n=3; hypertension n=36; cigarette pack years 49.4; ankle pressure on the treated limb 0mmHg n=6, 20mmHg n=10, 40mmHg n=25; ABI 0.340+/-0.187; TcPO2 on the treated foot 11.6mmHg (+/-6.7); walking ability unable to walk n=32, walk less than 50m n=9; mean walking distance 13m

CLI trial results

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, less than 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 VAS43.6 (n=47). At 6 months, 33.5 (on scale0-100) (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 (scale0-100, n=58). At 1 month 38.3 (n=47), At 6 months mean VAS 25.6 (scale0-100, n=42) At 12 months mean VAS 29.8 (scale0-100, n=38) At 18 months mean VAS 25.2 SE = 5 (scale0-100, 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	Nonsig between groups across 18 months
Pain outcome - McGill (details)	The pain-rating index (PRI), part I of the McGill
pain results McGill:	PRI baseline mean 22.6 (n = 57, SE = 1.5). At 1 month mean 17.9 (n=50), At 3 month mean 11.9 (n=39), at 6 months 13.2 (n=37), at 12 months

Trial name	**ESES**[68]
intervention group	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 month 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	nonsig 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
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) Nonsig at 18 months (p=0.70)
physical and functional abilities results limb salvage rates: intervention group	limb survival at 6 months 66%, at 1yr 60%, at 2yrs 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	limb survival at 6 months 68%, at 1yr 46%, at 2yrs 46%.

Trial name	ESES[68]
abilities results limb salvage rates : control group	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	nonsig 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=0·39 [70] Non sig 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 nonsig trend for lower rate of amputation p=0.08, ITT analysis p=0.17 (intermediate defined as transcutanous rest or peak oxygen pressure between 10 and 30mmHg, or not fitting into category of poor (Capillary microscopy: Low capillary density (density, <20/mm2), or: Low peak erythrocyte velocity (<50 mm/s), or: No reactive hyperemia (peak minus rest velocity, 0 or under mm/s). Laser Doppler scan perfusion: No reactive hyperemic response (peak – rest LDP, 3 or less AU)) or good (Capillary microscopy: Normal capillary density (density, 20 or more /mm2), and Present reactive hyperemia (peakv – restv, >0 mm/s) and Normal peak erythrocyte velocity (50 or more mm/s). Laser Doppler scan perfusion: Present reactive hyperemic response (peak – rest LDP, >3 AU)) [71]
Health-related quality of life outcome Nottingham health profile (details)	the first part of the NHP
health-related quality of life results Nottingham health profile: intervention group	baseline overall NHP mean 48 (SE2.6, n=57). 3 to 6 months decline of mean to 35 (SE2.6, 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-amp 40, amp 61.2 (n=29) overall 53.7; at 18 months non-amp 30.7, amp 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

Trial name	ESES[68]
	scores (p < 0.01).)
health-related quality of life results Nottingham health profile: control group	baseline overall NHP mean 47 (SE2.6, n=58). 3 to 6 months decline of mean to 34 (SE3, 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-amp 50.5, amp 57 overall 54 (n=23); at 18 months non-amp 49, amp 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 nonsig 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 EQ 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	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 EQ

Trial name	ESES[68]
results Euroqol: control group	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	nonsig 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), nonsig decline during follow-up
health-related quality of life results Sickness Impact Profile: control group	mean at intake 36 (SE = 1.9, n = 58), nonsig decline during follow-up
health-related quality of life results Sickness Impact Profile: comparison	nonsig between groups
Complications and adverse effects outcomes SCS group	Throughout 18 months follow-up, 25 surgery complication (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]

Trial name	**ESES**[68]
adverse effects: control group	Side-effects were reported in ten patients: upper gastrointestinal bleeding (3), nausea (7), dizziness (2). [70]
Deaths during follow-up period	Nonsig between groups. Disease-specific mortality at 6 months 5% in SCS group, 7% in control group; at 2 years 5% and 9% (p=0·45), respectively. Kaplan-Meier hazard ratio for the spinal-cord-stimulation 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, nonsig p=0.08 (p = 0.082) with a hazard ratio of 2.3. (most amputations within 1year after randomisation). Pain relief was sig better for SCS than control group p<0.001.[58]

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 9months 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.

Trial name	**Suy**[73]
physical and functional abilities results limb salvage rates : control group	Numbers of patients with excellent or good clinical result, at 9months 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 endpoints death without major amputation, or major amputation, nonsig between groups (p=0.42)
Complications and adverse effects outcomes SCS group	3 complications of SCS implantation: 1 infection led to removal and reimplantation of new device, 1 early disconnection requiring surgical connection, 1 late (2yrs after op) broken wire requiring surgical correction.
Deaths during follow-up period	4 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.

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 months follow-up ($p<0.05$), but no significant pain relief at 6 month or 12 months follow-up (too few observations at 18 months for analysis)

Trial name	**Jivegard**[74]
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	Nonsig between groups
Physical and functional abilities outcome - 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 STPI	Systolic toe to brachial pressure index

Trial name	**Jivegard**[74]
(details)	
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 sig 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 was 16, 8, 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 was 11, 8, 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%)

Trial name	**Jivegard**[74]
physical and functional abilities results limb salvage rates: comparison	nonsig 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 was reoperated for lead displacement. There were no infections, or other complications
Deaths during follow-up period	Intervention group 8 deaths (32%); Control group 8 deaths (31%)

Trial name	**Claeys**[76]
Physical and functional abilities outcome - ABI (details)	Ankle brachial index
physical and functional abilities results ABI : intervention group	At 12 months Increased by 0.03 (+10% on average from baseline) nonsig. (sig changes in ABI were only observed in SCS patients achieving complete ulcer healing +0.087+/-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	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

Trial name	**Claeys[76]**
abilities results ABI : comparison	
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) nonsig between groups for frequency of minor and major amputations
Complications and adverse effects outcomes SCS group	2 lead dislocations and 1 lead break, all corrected
adverse effects, group not specified	most common adverse reaction on PGE1 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	nonsig 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 TcpO2 >10mmHg in terms of ulcer healing

Appendix 6.4 Data extraction Angina

Angina Trial details

Trial name	**deJongste**[79]
Publication type of main ref (ie full report or abstract)	deJongste (1994) [79] Full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, Netherlands
Power calculation (priori sample calculation)	NR
Primary aim of study	To evaluate efficacy of SCS on exercise capacity and HRQoL in patients with intractable angina
Primary study outcome	Exercise capacity, HRQoL (daily and social activity scores)
Other study outcomes	Medication use - GTN intake, angina attacks, ECG, 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 weeks study period (then implanted with SCS)

Trial name	**ESBY**[82]
Publication type of main ref (ie full report or abstract)	Ekre 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 CABG in selected angina patients
Primary study outcome	Angina attacks, medication use – short-acting nitrates, number of patients taking medications
Other study outcomes	Exercise capacity, ECG, NHP, QLQ-AP, 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 (CABG)

Trial name	**SPiRiT**[83]
Publication type of main ref (ie full report or abstract)	McNab 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 PMR 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 (PMR)

Trial name	**Hautvast**[84]
Publication type of main ref (ie full report or abstract)	Hautvast 1998[84] Full report in peer-reviewed journal
Study design	Prospective RCT
Setting	Single centre, 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, HRQoL (LASA), ECG, 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 weeks study period)

Angina trial participants

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	8
Number receiving treatment according to allocation: control	9
Inclusion/exclusion criteria	Inclusion: 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 (SD 2.6)
Characteristics of participants at	Mean 63.2 (SD 3.6)

Trial name	**deJongste**[79]
baseline - control group: age	
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 (yrs) 9.8 (SD 0.8); angina (yrs) 2.5 (SD0.2); MI 8; PTCA 5; CABG 9; no. diseased vessels 2.8; LVEF 50.2 (SD11.9). Medication: CA-antagonist 8; beta-blocker 7; long-acting nitrates 8; aspirin/coumarin 8
Characteristics of participants at baseline - control group: other	Coronary artery disease (yrs) 10.9 (SD 1.0); angina (yrs) 2.8 (SD0.3); MI 10; PTCA 3; CABG 9; no. diseased vessels 2.5; LVEF 46.5 (SD13.4). Medication: CA-antagonist 9; beta-blocker 6; long-acting nitrates 9; aspirin/coumarin 9

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	Permanent implant n=50 (3 had CABG instead due to unstable angina[80])
Number receiving treatment according to allocation: control	N=49 (1 of these crossed over to SCS after 2 months[80])
Inclusion/exclusion criteria	Inclusion: Coronary artery disease Severe angina pectoris, despite optimal pharmacological treatment. 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 to manage 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 (range 42-82)
Characteristics of participants at	mean 68.7 (range 40-81)

Trial name	**ESBY**[82]
baseline - control group: age	
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, n 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%) Previous CABG, n= 14 (26%). One-vessel disease, n= 5 (9%) Two-vessel disease, n=14 (26%) Three-vessel disease, n=34 (64%)

Trial name	**ESBY**[82]
	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) Ejection fraction (EF), mean (range) 0·58 (0·26–0·82) Percentage of patients with EF >0·4 83% History, n 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	Two of 104 subjects worked full-time, five worked part-time, 21 were on sick leave and 76 had retired. The mean Higgin's

Trial name	**ESBY**[82]
baseline - group not indicated	score (a scoring system for estimation of pre-operative risk) was just above four 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]

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	32 (1 refused, 1 had control treatment)
Number receiving treatment according to allocation: control	33 (1 refused)
Inclusion/exclusion criteria	Inclusion: 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 99 m sestamibi-technetium scanning. Exclusion criteria: myocardial wall thickness <8 mm in the areas to be

Trial name	**SPiRiT**[83]
	treated by PMR, implanted pacemakers or defibrillators or comorbidity 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 (SD 7.3)
Characteristics of participants at baseline - control group: age	mean 62.9 (SD 9.6)
Characteristics of participants at baseline - intervention group: sex	5 female; 29 male
Characteristics of participants at baseline - control group: sex	3 female; 31 male
Characteristics of participants at baseline - intervention group: other	Previous revascularisation PTCA 6 (18%) Stents 6 (18%) CABG 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%)

Trial name	SPiRiT[83]
	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)
Characteristics of participants at baseline - control group: other	Previous revascularisation PTCA 10 (29%) Stents 6 (18%) CABG 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

Trial name	SPiRiT[83]
	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)

Trial name	Hautvast[84]
Number randomised (total)	25
Number randomised: intervention group	13
Number randomised: control group	12

Trial name	**Hautvast**[84]
Number receiving treatment according to allocation: intervention	13
Number receiving treatment according to allocation: control	12
Inclusion/exclusion criteria	Inclusion: 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 were the inability to perform an exercise test, cardiac conduction disturbances disabling recognition of ischemia on the electrocardiogram, and the anatomic inability to accept stimulator implantation, aged over 75, LVEF<30%.
Characteristics of participants at baseline - intervention group: age	mean age 62 (SD 8)
Characteristics of participants at baseline - control group: age	mean age 63 (SD 7)
Characteristics of participants at baseline - intervention group: sex	7 female; 6 male
Characteristics of participants at baseline - control group: sex	4 female; 8 male
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); No. of stenosed coronary arteries mean 2.1 (SD 0.6); Total myocardial infarctions 6;

Trial name	**Hautvast**[84]
	Total coronary bypass surgeries 10; Total coronary angioplasties 12; Medication - Beta-Blockers n=12 Calcium reentry 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); No. of stenosed coronary arteries mean 2.5 (SD 0.5); Total myocardial infarctions 11; Total coronary bypass surgeries 13; Total coronary angioplasties 3; Medication - Beta-Blockers n=11 Calcium reentry blockers n=11 Long-acting nitrates n=12

Angina trial results

Trial name	**deJongste**[79]
Medication use outcome - details	amount of sublingual glyceryl trinitrate intake, registered in a diary during 2weeks, 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), sig 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 sig diff 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 2weeks, 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) sig 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	angina pectoris per week sig diff change from baseline SCS vs control group p<0.05

Trial name	**deJongste**[79]
abilities results angina : comparison	
physical and functional abilities outcome - electrocardiograph	left ventricular ejection fraction, 24-hr 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-hr 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 1week. 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, endpoints angina pain, fatigue, shortness of breath, onset of threatening arrhythmia or exertional hypotension
physical and functional abilities results exercise capacity : intervention group	exercise duration(s) mean (SE) baseline 659 (+/- 121), 6-8 weeks 827 (+/-138), sig change from baseline $p<0.05$. rate-pressure product (beats/min^{-1} x mmHg x10^{3}) baseline mean(SE) 12.9(+/-0.75), 6-8 weeks 13.8(+/-1.3) , sig change from baseline $p<0.05$. time to angina (s) mean (SE) baseline 520 (+/-138), 6-8 weeks 691 (+/-174), sig 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) , sig 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), sig change from baseline $p<0.05$.
physical and functional abilities results exercise capacity : control group	exercise duration(s) mean (SE) baseline 705 (+/- 136); 6-8 weeks 694 (+/-67). rate-pressure product (beats/min^{-1} x mmHg x10^{3}) baseline mean(SE) 14.8(+/-9.1), 6-8 weeks 14.2(+/-13.9) . time to angina (s) 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

Trial name	**deJongste**[79]
	weeks 0.11(+/-0.02) .
physical and functional abilities results exercise capacity : comparison	exercise duration sig diff between change in SCS group vs change in control group p<0.03. ST depression at maximal exercise sig diff between change in SCS group vs change in control group p<0.02. Time to angina sig diff between change in SCS group vs change in control group p<0.05. Other variables nonsig 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
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) sig 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) sig diff between change in SCS group vs change in control group p<0.05. SAS sig diff between change in SCS group vs change in control group p<0.05.
Complications and adverse effects outcomes SCS group	no adverse events during the 6-8 week study period

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	sig reduction (p<0.0001) in short-acting nitrates at 6 months, no other sig differences. Number of patients taking drug at baseline, at 6 months - 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) sig reduction from baseline p<0.0001[80]
Medication use results : control group	sig 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 sig differences. Short-acting nitrates 47 13, Long-acting nitrates 43 8, beta -blockers 43 24,

Trial name	**ESBY**[82]
	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) sig reduction from baseline $p<0.0001$[80]
Medication use results : comparison between groups	there was sig more reduction for 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 ($p<0.0001$). Nonsig 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	83.7% had a good self-estimated treatment effect (better or symptom free). Angina attack frequency, attacks/wk baseline mean 14.6 (SD 13.5), follow-up mean 4.4 (SD7.4) sig reduction $p<0.0001$[80]

Trial name	**ESBY**[82]
results angina : intervention group	
physical and functional abilities results angina : control group	79.5% had a good self-estimated treatment effect. Angina attack frequency, attacks/wk baseline mean 16.2 (SD 12.6) follow-up mean 5.2 (SD 10.3) sig reduction p<0.0001[80]
physical and functional abilities results angina : comparison	Nonsig between groups for self-estimated treatment effect, or for frequency of angina attacks [80]
physical and functional abilities outcome - electrocardiograph	Holter ECG: 24-hr ambulatory ECG at baseline and 6 months SCS group had stimulation discontinued 24hours 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 (SD32.1) Follow-up 29.1 (SD30.8), ischemic burden mean baseline 22.7 (SD39.3) follow-up 44.2 (SD124.2). 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 (SD12.6) follow-up 97.3(SD13.4), LVH index (mm) mean baseline 13.3 (SD6.4) follow-up 13.1 (SD6.3), MI score mean baseline 1.0 (SD1.1) follow-up 1.1 (SD1.1). (n=48) heart frequency (beats per minute) mean baseline 66.5 (SD 9.8) follow-up 64.9 (SD9.4), heart rate variability (ms) mean baseline 545.0 (SD 184.0) follow-up 540.6 (SD192.5) [80]
physical and functional abilities	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 (SD39.9) Follow-up 17.8 (SD21.4), ischemic burden mean baseline 47.6 (SD124.6) follow-up

Trial name	**ESBY**[82]
electrocardiograph results : control group	23.8(SD78.5) . 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(SD1.3). Resting ECG (n=29) QRS duration (ms) mean baseline 97.2 (SD13.1) follow-up 98.5(SD15.0), LVH index (mm) mean baseline 13.1 (SD5.7) follow-up 15.4 (SD5.8), MI score mean baseline 1.2 (SD1.3) follow-up 1.5 (SD1.3). (n=35) heart frequency (beats per minute) mean baseline 66.5 (SD 8.1) follow-up 72.4 (SD10.6), heart rate variability (ms) mean baseline 542.6(SD 125.7) follow-up 464.3 (SD176.7) [80]
physical and functional abilities electrocardiograph results : comparison	SCS sig more number ($p<0.05$) and duration ($p=0.02$) of ischaemic episodes than control. Nonsig between groups for number of angina attacks. Nonsig 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 dyspnea rated 6 to 7 of 10, or showed signs of severe myocardial ischemia 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 had shown that SCS could increase tolerance to pacing[102])
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) nonsig from baseline; ST-segment depression on maximum workload, mm -22.01 (1.17) -21.95 (1.18) nonsig from baseline; ST-segment depression on comparable workload, mm -21.73 (1.14) -21.66 (1.24) nonsig from baseline; Rate pressure product (RPP) on maximum workload, mm Hg/minx10(to the power of 3) 21.4 (5.8) 21.2 (6.9) nonsig from baseline; RPP on comparable workload, mm Hg/minx10(to the power of 3) 20.9 (5.7) 20.6 (6.5) nonsig from baseline[80]

Trial name	**ESBY**[82]
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) sig increase p=0.002; ST-segment depression on maximum workload, mm -21.46 (1.36) -20.68 (1.52) sig reduction p=0.0009; ST-segment depression on comparable workload, mm -21.40 (1.39) -20.46 (1.13) sig reduction p=0.0001; Rate pressure product (RPP) on maximum workload, mm Hg/minx10(to the power of 3) 21.6 (5.4) 25.4 (5.6) sig increase p=0.0001; RPP on comparable workload, mm Hg/minx10(to the power of 3) 21.3 (5.4) 23.0 (5.4) sig 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)	NHP two parts.
health-related quality of life	In both quality of life assessments there were significant improvements 6 months after SCS/CABG compared to run-in (P<0·001), and the results were consistent after

Trial name	ESBY[82]
results Nottingham health profile: intervention group	58 months. Sig 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<0·001), and the results were consistent after 58 months. Sig 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:	Significant improvements 6 months after SCS compared to run-in (P<0·001), and the results were consistent after 4·8 years. Sig improvements in all four subcategories

Trial name	**ESBY**[82]
intervention group	
health-related quality of life results QLQ-AP: control group	Significant improvements 6 months after CABG compared to run-in (P<0·001), and the results were consistent after 4·8 years. Sig improvements in all four subcategories
health-related quality of life results QLQ-AP: comparison	At 6 months and 58 months, nonsig between groups
Complications and adverse effects outcomes SCS group	During the follow-up time, 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. 8 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 nonfatal 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<0·02) however 3 of the deaths in the CABG group had occurred prior to surgery. At 3 and 5 years, there were no significant differences between the groups. 3 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

Trial name	ESBY[82]
	of 51 (68·6%) in the CABG group. Sixty-six percent of the deaths were cardiac deaths, without significant difference between the groups.

Trial name	SPiRiT[83]
Physical and functional abilities outcome - rest angina episodes / angina attacks / angina class	angina class as measured by the 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 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).

Trial name	**SPiRiT**[83]
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%)
physical and functional abilities results exercise	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 =

Trial name	SPiRiT[83]
capacity : comparison	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 nonsig 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 (nonsig)
health-related quality of life results SF36: control group	some improvements at 3 and 12 months (nonsig)
health-related quality of life results SF36: comparison	Nonsig between groups
health-related quality of life Seattle angina questionnaire details	disease-specific Seattle Angina Questionnaire
health-related quality of life	some improvements at 3 and 12 months (nonsig)

Trial name	SPiRiT[83]
results Seattle angina questionnaire: intervention group	
health-related quality of life results Seattle angina questionnaire: control group	some improvements at 3 and 12 months (nonsig)
health-related quality of life results Seattle angina questionnaire: comparison	Nonsig 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 pseudo-aneurysm, which resolved within 24 h. Follow-up Twenty-six 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

Trial name	SPiRiT[83]
	adverse events 24 were classed as severe
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 that they either required admission, prolonged stay in hospital, required surgery, were life threatening or ultimately resulted in death.
Deaths during follow-up period	6 deaths: 4 in the SCS group (ischaemic heart disease, metastatic squamous cell carcinoma, presumed malignancy, and acute MI). 2 deaths in control group (stomach carcinoma, and ischaemic heart disease/MI).

Trial name	Hautvast[84]
Pain outcome - VAS (details)	VAS 0-10cm, Two 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 sig diff 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	nonsig between groups
Medication use outcome - details	patient diary: Two weeks before the first baseline tests and during the

Trial name	Hautvast[84]
	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 sig diff 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: Two 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 sig diff 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 (-17-1) sig diff 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 (- 54.9-8.5) sig diff from baseline p=0.01. Total ischemic burden (mm x min, median and range) baseline 22.2 (0- 1583), 6 weeks 0.0 (0- 123.8),

Trial name	Hautvast[84]
	difference (%) -19.4 (-1555.8- 19.8) sig diff from baseline p=0.01. At baseline, 9 subjects in the treatment group had ischemic episodes on the 48-hour electrocardiogram. 1 patient in the treatment group had no ischemic 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 - 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 - 96.2). Total ischemic burden (mm x min, median and range) baseline 1.2 (0- 589), 6 weeks 2.7 (0- 244.8), difference (%) 0.3 (-589 - 197.8). At baseline, 6 patients in the control group had ischemic episodes on the 48-hour electrocardiogram. 3 patients in the control group had no ischemic episodes both at baseline and after 6 weeks.
physical and functional abilities electrocardiograph results : comparison	number of ischaemic episodes sig diff between groups p=0.04. nonsig 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 with in 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 sig diff from baseline p=0.03; Total exercise duration (seconds) baseline 453±156, 6 weeks 533 ± 184, difference (%) 19±24 sig diff 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 (mm Hg x 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 sig diff from baseline p=0.04; Rate-pressure product at comparable workload (mm Hg x 100/min) baseline 161 ±48, 6 weeks 150±57, difference (%) -3 ± 37
physical and functional abilities	treadmill exercise tests: time to angina (seconds) baseline 287±119, 6 weeks 246±97, difference (%) -9±21; Total exercise duration

Trial name	**Hautvast**[84]
results exercise capacity : control group	(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 (mm Hg x 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 (mm Hg x 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 0-10cm 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 sig diff 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	nonsig between groups
Complications and adverse effects outcomes SCS group	no complications
adverse effects: control group	no complications

Appendix 7: Eddy/BMJ check lists for the published cost effectiveness studies

Eddy/BMJ checklist for quality of studies

	Taylor & Taylor	
A statement of the problem;	Y	
A discussion of the need for modelling vs alternative methodologies	Y	
A description of the relevant factors and outcomes (disease-specific);	Y	
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 sub-model	Y	
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;	Y	
A list of assumptions pertaining to: the structure of the model (eg. factors included, relationships, and distributions) and the data;	Y It is not clear in some cases	
A list of parameter values that will be used for a basecase analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	Y	
The results derived from applying the model for the basecase;	Y The results are not presented in ICERs	
"The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold."	Y One-way sensitivity analyses were performed	

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	Y One-way sensitivity analyses are not optimal	
"A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity. "	NA	
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;	Y for the description of the settings N for the factors that could limit the applicability	
A description of research in progress that could yield new data that could alter the results of the analysis	N	

Y – yes; N – no; NA – not applicable

Eddy/BMJ checklist for modelling assessment

	ABHI
A statement of the problem;	Y
A discussion of the need for modelling vs alternative methodologies	N
A description of the relevant factors and outcomes (disease-specific)	Y
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 sub-model	Y
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	Y The authors not always give a detailed description of the parameters considered
A list of assumptions pertaining to: the structure of the model (eg. factors included, relationships, and distributions) and the data	Y It is not clear in some cases
A list of parameter values that will be used for a basecase analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis	Y
The results derived from applying the model for the basecase	Y The basecase varies depending on the analysis
"The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold."	Y Univariate and probabilistic sensitivity analyses were performed
A discussion of how the modelling assumptions might affect the results,	Y There is a small

indicating both the direction of the bias and the approximate magnitude of the effect	discussion of the modelling assumptions and their impact
"A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity. "	NA
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	Y for the description of the settings N for the factors that could limit the applicability
A description of research in progress that could yield new data that could alter the results of the analysis	N

Y – yes; N – no; NA – not applicable

Appendix 8: Schematic models of decision tree and Markov model in the ABHI submission

Figure 12: Six-month decision tree for SCS+CMM vs CMM in FBSS and CRPS

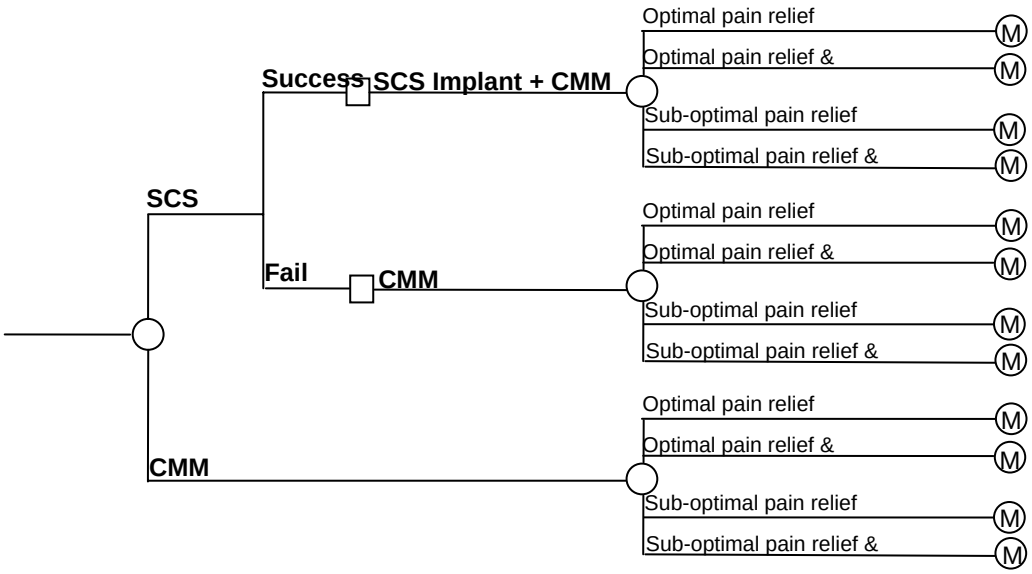


Figure 13: Six-month decision tree for SCS+CMM vs re-operation in FBSS

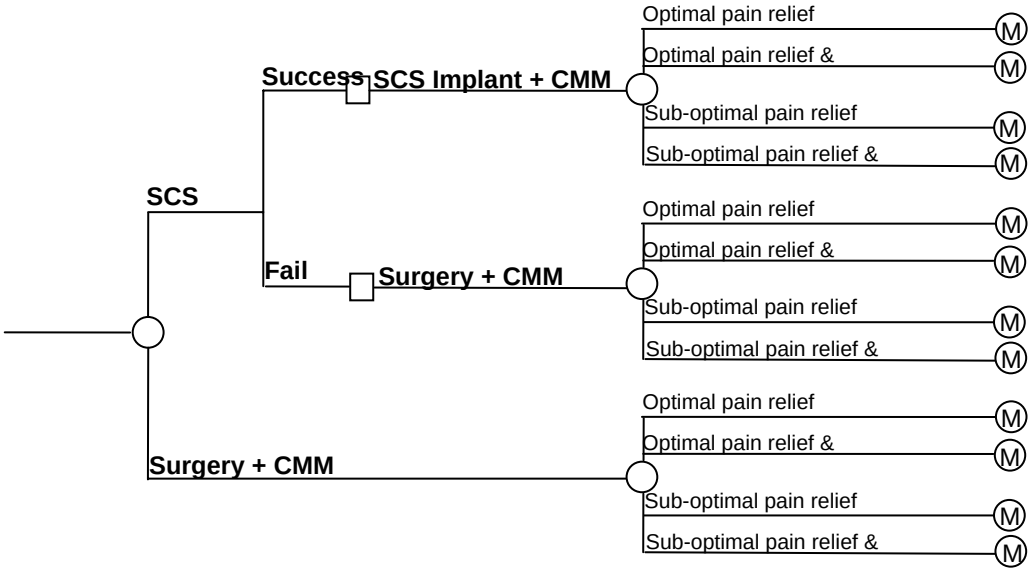


Figure 14: Schematic of the long-term Markov Model for FBSS

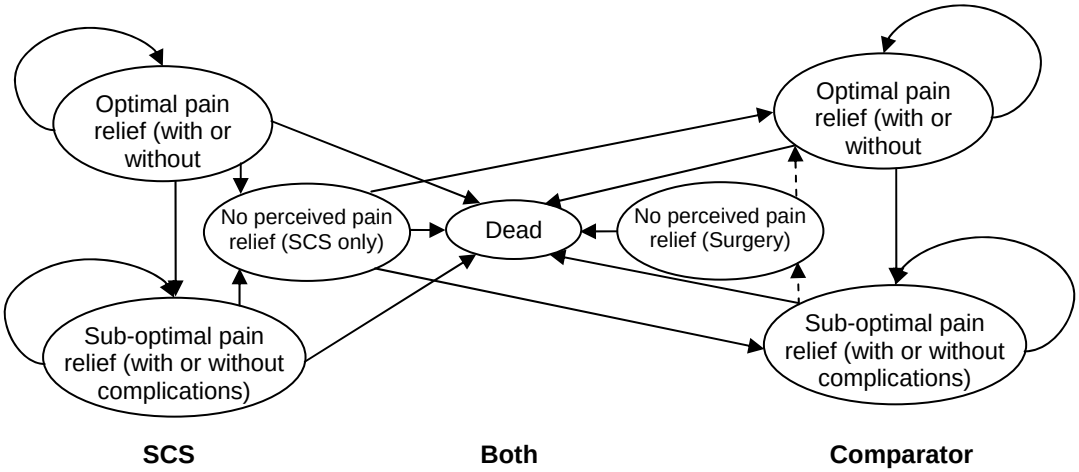
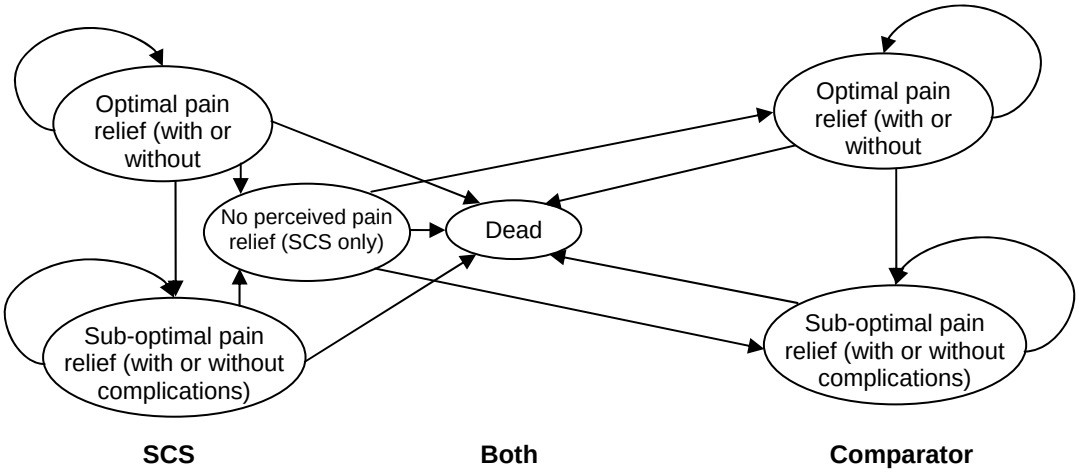


Figure 15: Schematic of the long-term Markov Model for FBSS



Appendix 9: SCS Devices Price List

Implant

Medtronic Neurostimulation System Price List

Model number	Restore ADVANCED System	
37713	Implantable neursostimulator	[redacted]
37742	External patient programmer	[redacted]
	Total	[redacted]
37702	Implantable neursostimulator	[redacted]
37742	External patient programmer	[redacted]
	Total	[redacted]
	Synergy EZ System	
7427	Implantable neursostimulator	[redacted]
7435	External patient programmer	[redacted]
	Total	[redacted]
	Synergy Veristrel System	
7427V	Implantable neursostimulator	[redacted]
7435	External patient programmer	[redacted]
	Total	[redacted]
	Itrel 3 System	
7425	Implantable neursostimulator	[redacted]
7434	External patient programmer	[redacted]
	Total	[redacted]
Boston Scientific Company		
SC-1110	Implantable neursostimulator	[redacted]
	Remote Control	[redacted]
	Kit- Charger	[redacted]
	Total	[redacted]

Appendix 10: Sensitivity Analysis Parameters

Variable description	Mean	Distribution	SE	Lower	Upper	Alpha	Beta	n	
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.* [59]
SCS % with complications	0.3170	Beta	0.016173	0.2853	0.3487	13	28	41	Kumar *et al.* [59]
SCS: 50% pt Optimal pain relief	0.5854	Beta	0.029872	0.5268	0.6439	24	17	41	Kumar *et al.* [59]
CMM_noTrial	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.* [59]
FBSS: SCS+ CMM vs Re-operation									
SCS Trial Success_re-operation	0.7730	Beta	0.039439	0.6957	0.8503	17	6	23	North *et al.* [130]
SCS % with complications_re-operation	0.3170	Beta	0.016173	0.2853	0.3487	13	28	41	Kumar *et al.* [59]
SCS: 50% pt Optimal pain relief_re-operation	1.0000	Constant	0.029872	0.5268	0.6439	17	0	17	North *et al.* [130]
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.* [59]

SCS: 50% pt Optimal pain relief_CRPS	0.7500	Beta	0.038265	0.675	0.825	18	6	24	Kemler *et al.* [65]
CRPS:CMM % with complications	0.0000	Constant	1	0	0				Fritzell *et al.* [113]
CRPS:CMM: 50% pt Optimal pain relief	0.4444	Beta	0.022679	0.4	0.4889	8	10	18	Assumption
Utilities									
FBSS: SCS+CMM vs CMM									
SCS vs CMM Optimal pain relief 50% pt	0.598	Beta	0.030612	0.538	0.658	154	103	257	PROCESS
SCS vs CMM Optimal pain relief & complications 50% pt	0.528	Beta	0.027041	0.475	0.581	181	162	342	PROCESS
SCS vs CMM Sub-optimal pain relief 50% pt	0.258	Beta	0.013265	0.232	0.284	285	819	1104	PROCESS
SCS vs CMM Sub-optimal pain relief & complications 50% pt	0.258	Beta	0.013265	0.232	0.284	285	819	1104	PROCESS
SCS vs CMM failure 50% pt	0.168	Beta	0.008673	0.151	0.185	319	1582	1901	PROCESS
FBSS: SCS+ CMM vs Re-operation									
SCS vs reoperation Optimal pain relief 50% pt	0.598	Beta	0.030612	0.538	0.658	154	103	257	PROCESS
SCS vs reoperation Optimal pain relief & complications 50% pt	0.528	Beta	0.027041	0.475	0.581	181	162	342	PROCESS
SCS vs reoperation Sub-optimal pain relief 50% pt	0.258	Beta	0.013265	0.232	0.284	285	819	1104	PROCESS
SCS vs reoperation Sub-optimal pain relief & complications 50% pt	0.258	Beta	0.013265	0.232	0.284	285	819	1104	PROCESS
SCS vs reoperation failure 50% pt	0.168	Beta	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	Mc Dermott *et al.* [16]
CRPS:SCS vs CMM Optimal pain relief & complications 50% pt	0.62	Beta							
CRPS:SCS vs CMM Sub-optimal pain relief 50% pt	0.46	Beta				305	297	602	Mc Dermott *et al.* [16]
CRPS:SCS vs CMM Sub-optimal pain relief & complications 50% pt	0.41	Beta							
CRPS:SCS vs CMM failure 50% pt	0.16	Beta				138	464	602	Mc Dermott *et al.* [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.*[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.* [59]
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 opti to subopti	0	Constant							
Annual probability of failing SCS	0.0324	Normal	0.042857	0	0.168				Kumar *et al.* [112]
CMM Annual movement from opti to subopti	0	Constant							
FBSS: SCS+CMM vs re-operation									
Re-operation annual % patients	0.0500	Beta	0.002551	0.045	0.055	365	6933	7298	Assumption
% patients optimal pain relief after re-operation	0.1900	Beta	0.009694	0.171	0.209	3	13	16	
Cost parameters									
Average cost of failed screening	£1,041	Av_cost_fail_screen	Constant						Kumar *et al.* [116]
Average cost per trial stimulation	£4,156	Av_cost_screen	Normal	2646	3997	4315			Kumar *et al.* [116]
Average cost of implant	£10,479	Av_cost_implant	Normal	5316	7854	13104			Kumar *et al.* [116]
Average cost of CMM (6 months), SCS+CMM	£1,720	Av_cost_CMM_SCSCMM	Constant						Kumar *et al.* [59]
Average cost of CMM (6 months), CMM alone	£3,468	Av_cost_CMM_CMMalone	Constant						Kumar *et al.* [59]
Average cost of CMM (year 2 to 15)	£5,704								Varies in terms of CMM cost reduction
Cost reduction of CMM alone after year 1	0.178	Cost_red_adverse_ev_y1	Triangular	0.013592	0.15096	0.20424			Kumar *et al.* [110]
Cost of adverse events over 6 months	£388	Cost_adverse_ev	Constant						Kumar *et al.* [116]
Cost of adverse events subsequent cycles	£95								Assumption
Cost of re-operation	£4,252	Cost_reop	Normal	226.0204	3987	4873			NHS National Tariff R09 [111]

Average cost of CMM (6 months), CRPS:SCS+CMM	£1,691	Av_cost_CRPS_SCSCMM	Constant						Kumar *et al*. [59]
Average cost of CMM (6 months), CRPS:CMM alone	£3,468	Av_cost_CRPS_CMMalone	Constant						Kumar *et al*. [59]
Average cost of re-implant	£10,479		Normal	5316	7854	13104			Kumar *et al*. [116]
Cost of adverse events over 6 months (re-implant)	£388		Constant						Kumar *et al*. [116]
Device removal	£1,041		Constant						Kumar *et al*. [116]

Appendix 11: Discounted costs and QALYs

Results using different device longevity values

FBSS: SCS+CMM vs 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	£7,996	£10,035	1.26	£7,673	£10,203	1.33
5	£3,574	£4,491	1.26	£3,155	£4,201	1.33
6	£2,913	£3,661	1.26	£2,591	£3,451	1.33
7	£2,304	£2,896	1.26	£2,065	£2,750	1.33
8	-£1,267	-£1,594	1.26	-£1,720	-£2,293	1.33
9	-£1,492	-£1,878	1.26	-£1,912	-£2,549	1.33
10	-£1,707	-£2,147	1.26	-£2,096	-£2,794	1.33
11	-£1,910	-£2,403	1.26	-£2,272	-£3,029	1.33
12	-£2,103	-£2,647	1.26	-£2,440	-£3,254	1.33
13	-£2,287	-£2,878	1.26	-£2,602	-£3,470	1.33
14	-£2,461	-£3,098	1.26	-£2,757	-£3,676	1.33
15	-£5,787	-£7,289	1.26	-£6,333	-£8,453	1.33

FBSS: SCS+CMM vs re-operation

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	£7,043	£9,430	1.34	£6,771	£9,625	1.42
5	£3,167	£4,248	1.34	£2,819	£4,015	1.42
6	£2,588	£3,472	1.34	£2,326	£3,314	1.42
7	£2,055	£2,757	1.34	£1,866	£2,659	1.42
8	-£1,071	-£1,440	1.34	-£1,440	-£2,055	1.43
9	-£1,269	-£1,705	1.34	-£1,608	-£2,294	1.43
10	-£1,456	-£1,957	1.34	-£1,768	-£2,523	1.43
11	-£1,634	-£2,196	1.34	-£1,922	-£2,743	1.43
12	-£1,803	-£2,424	1.34	-£2,069	-£2,953	1.43
13	-£1,964	-£2,640	1.34	-£2,210	-£3,155	1.43
14	-£2,116	-£2,845	1.34	-£2,345	-£3,348	1.43
15	-£5,024	-£6,763	1.35	-£5,466	-£7,813	1.43

CRPS: SCS+CMM vs 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	£8,775	0.35	£24,137	£8,942	0.37
5	£12,264	£4,306	0.35	£11,029	£4,103	0.37
6	£10,351	£3,637	0.35	£9,398	£3,498	0.37
7	£8,591	£3,020	0.35	£7,877	£2,933	0.37
8	-£1,701	-£600	0.35	-£3,030	-£1,132	0.37
9	-£2,349	-£829	0.35	-£3,581	-£1,338	0.37
10	-£2,965	-£1,046	0.35	-£4,109	-£1,536	0.37
11	-£3,549	-£1,252	0.35	-£4,614	-£1,725	0.37
12	-£4,104	-£1,449	0.35	-£5,099	-£1,907	0.37
13	-£4,632	-£1,635	0.35	-£5,563	-£2,081	0.37
14	-£5,133	-£1,812	0.35	-£6,008	-£2,247	0.37
15	-£14,658	-£5,191	0.35	-£16,248	-£6,098	0.38

Results using different device cost values

FBSS: SCS+CMM vs CMM alone

Device Cost	Discounted ICER (£/QALY)	Discounted Incremental cost (£)	Discounted Incremental QALY	Undiscounted ICER (£/QALY)	Undiscounted Incremental cost (£)	Undiscounted Incremental QALY
£5,000	£2,563	£3,216	1.26	£2,282	£3,035	1.33
£6,000	£4,542	£5,700	1.26	£4,246	£5,646	1.33
£7,000	£6,521	£8,184	1.26	£6,210	£8,258	1.33
£8,000	£8,500	£10,668	1.26	£8,173	£10,869	1.33
£9,000	£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

FBSS: SCS+CMM vs re-operation

Device Cost	Discounted ICER (£/QALY)	Discounted Incremental cost (£)	Discounted Incremental QALY	Undiscounted ICER (£/QALY)	Undiscounted Incremental cost (£)	Undiscounted Incremental QALY
£5,000	£2,283	£3,056	1.34	£2,057	£2,925	1.42
£6,000	£4,017	£5,378	1.34	£3,775	£5,366	1.42
£7,000	£5,751	£7,700	1.34	£5,492	£7,807	1.42
£8,000	£7,485	£10,022	1.34	£7,209	£10,248	1.42
£9,000	£9,219	£12,344	1.34	£8,926	£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

CRPS: SCS+CMM vs CMM alone

Device Cost	Discounted ICER (£/QALY)	Discounted Incremental cost (£)	Discounted Incremental QALY	Undiscounted ICER (£/QALY)	Undiscounted Incremental cost (£)	Undiscounted Incremental QALY
£5,000	£9,374	£3,278	0.35	£8,537	£3,163	0.37
£6,000	£15,101	£5,280	0.35	£14,220	£5,268	0.37
£7,000	£20,828	£7,283	0.35	£19,903	£7,374	0.37
£8,000	£26,555	£9,286	0.35	£25,586	£9,479	0.37
£9,000	£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

Impact of device average price and device longevity on ICER

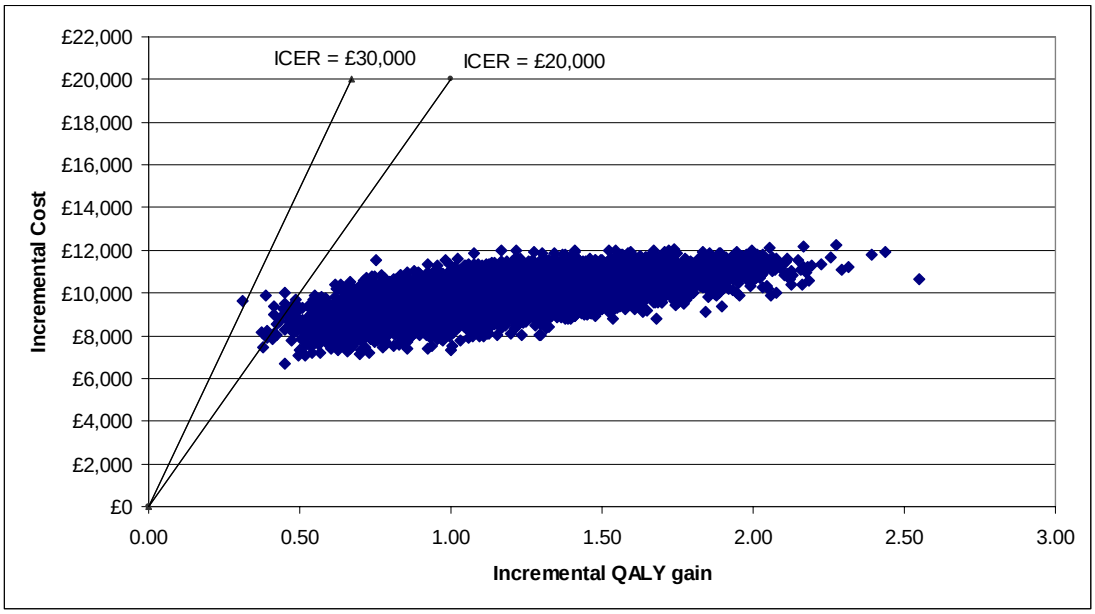
FBSS: SCS+CMM vs re-operation	Discounted ICER (£/QALY)										
Device Cost/ Longevity	£5,000	£6,000	£7,000	£8,000	£9,000	£10,000	£11,000	£12,000	£13,000	£14,000	£15,000
1	£37,142	£43,429	£49,715	£56,001	£62,288	£68,574	£74,861	£81,147	£87,434	£93,720	£100,006
2	£14,424	£17,744	£21,063	£24,383	£27,703	£31,022	£34,342	£37,662	£40,981	£44,301	£47,621
3	£5,583	£7,749	£9,914	£12,079	£14,244	£16,409	£18,575	£20,740	£22,905	£25,070	£27,235
4	£2,283	£4,017	£5,751	£7,485	£9,219	£10,953	£12,687	£14,421	£16,156	£17,890	£19,624
5	-£570	£791	£2,153	£3,514	£4,876	£6,238	£7,599	£8,961	£10,322	£11,684	£13,046
6	-£997	£309	£1,615	£2,921	£4,227	£5,533	£6,839	£8,145	£9,451	£10,757	£12,063
7	-£1,389	-£135	£1,120	£2,374	£3,629	£4,884	£6,138	£7,393	£8,648	£9,902	£11,157
8	-£3,690	-£2,736	-£1,782	-£828	£126	£1,080	£2,034	£2,988	£3,943	£4,897	£5,851
9	-£3,836	-£2,900	-£1,965	-£1,030	-£95	£840	£1,775	£2,711	£3,646	£4,581	£5,516
10	-£3,974	-£3,056	-£2,139	-£1,222	-£305	£612	£1,529	£2,447	£3,364	£4,281	£5,198
11	-£4,105	-£3,204	-£2,304	-£1,404	-£504	£396	£1,296	£2,196	£3,096	£3,996	£4,896
12	-£4,229	-£3,345	-£2,461	-£1,578	-£694	£190	£1,074	£1,958	£2,841	£3,725	£4,609
13	-£4,347	-£3,479	-£2,611	-£1,742	-£874	-£5	£863	£1,731	£2,600	£3,468	£4,336
14	-£4,460	-£3,606	-£2,752	-£1,899	-£1,045	-£191	£663	£1,516	£2,370	£3,224	£4,077

CRPS: 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	£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	£9,374	£15,101	£20,828	£26,555	£32,282	£38,010	£43,737	£49,464	£55,191	£60,918	£66,646
5	-£51	£4,435	£8,921	£13,408	£17,894	£22,380	£26,866	£31,352	£35,839	£40,325	£44,811
6	-£1,456	£2,845	£7,147	£11,448	£15,749	£20,050	£24,352	£28,653	£32,954	£37,256	£41,557
7	-£2,749	£1,382	£5,513	£9,644	£13,775	£17,906	£22,037	£26,168	£30,299	£34,430	£38,561
8	-£10,309	-£7,173	-£4,037	-£902	£2,234	£5,370	£8,505	£11,641	£14,776	£17,912	£21,048
9	-£10,784	-£7,711	-£4,639	-£1,566	£1,507	£4,580	£7,653	£10,726	£13,799	£16,872	£19,945
10	-£11,236	-£8,223	-£5,210	-£2,196	£817	£3,831	£6,844	£9,858	£12,871	£15,884	£18,898
11	-£11,666	-£8,709	-£5,752	-£2,795	£162	£3,119	£6,076	£9,033	£11,989	£14,946	£17,903
12	-£12,074	-£9,170	-£6,267	-£3,364	-£461	£2,442	£5,346	£8,249	£11,152	£14,055	£16,958
13	-£12,461	-£9,609	-£6,757	-£3,904	-£1,052	£1,800	£4,652	£7,504	£10,357	£13,209	£16,061
14	-£12,829	-£10,025	-£7,221	-£4,418	-£1,614	£1,190	£3,994	£6,797	£9,601	£12,405	£15,209

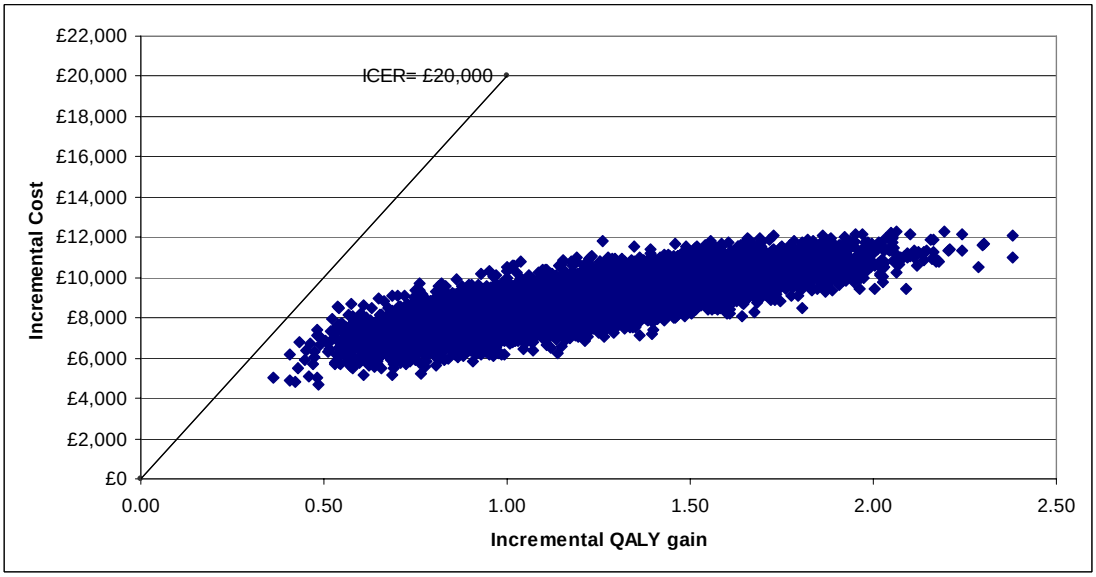
CRPS: SCS+CMM vs CMM alone	Undiscounted ICER (£/QALY)										
Device Cost/ Longevity	£5,000	£6,000	£7,000	£8,000	£9,000	£10,000	£11,000	£12,000	£13,000	£14,000	£15,000
1	£128,358	£149,821	£171,284	£192,747	£214,210	£235,673	£257,136	£278,599	£300,062	£321,525	£342,989
2	£49,658	£60,757	£71,855	£82,954	£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	£8,537	£14,220	£19,903	£25,586	£31,269	£36,952	£42,635	£48,317	£54,000	£59,683	£65,366
5	-£1,090	£3,325	£7,740	£12,155	£16,569	£20,984	£25,399	£29,814	£34,229	£38,644	£43,059
6	-£2,288	£1,969	£6,227	£10,484	£14,741	£18,998	£23,256	£27,513	£31,770	£36,027	£40,284
7	-£3,405	£705	£4,815	£8,925	£13,035	£17,145	£21,255	£25,365	£29,475	£33,585	£37,695
8	-£11,416	-£8,361	-£5,306	-£2,251	£804	£3,859	£6,914	£9,969	£13,024	£16,079	£19,134
9	-£11,821	-£8,819	-£5,817	-£2,815	£186	£3,188	£6,190	£9,192	£12,193	£15,195	£18,197
10	-£12,208	-£9,258	-£6,307	-£3,356	-£405	£2,545	£5,496	£8,447	£11,397	£14,348	£17,299
11	-£12,580	-£9,678	-£6,776	-£3,874	-£972	£1,929	£4,831	£7,733	£10,635	£13,537	£16,438
12	-£12,936	-£10,081	-£7,226	-£4,371	-£1,516	£1,339	£4,194	£7,049	£9,904	£12,759	£15,614
13	-£13,277	-£10,466	-£7,656	-£4,846	-£2,036	£774	£3,584	£6,394	£9,204	£12,014	£14,824
14	-£13,603	-£10,836	-£8,069	-£5,302	-£2,535	£232	£2,999	£5,766	£8,533	£11,300	£14,067

Appendix 12: Probabilistic Sensitivity Analyses

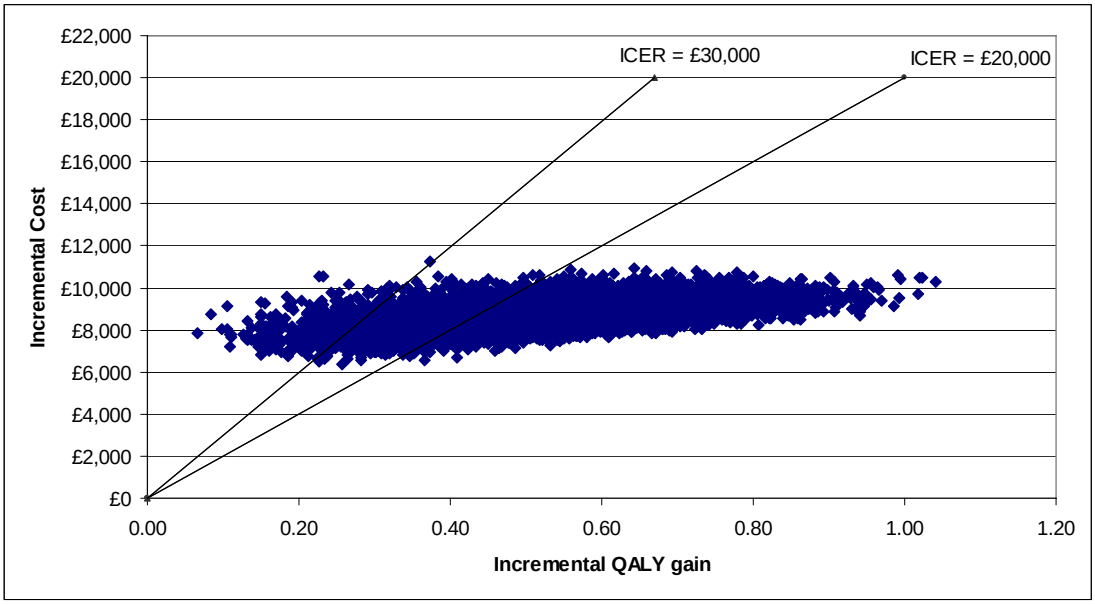
Scatter plot of base case results for FBSS: SCS+CMM vs CMM alone



Scatter plot of base case results for FBSS: SCS+CMM vs re-operation



Scatter plot of base case results for CRPS: SCS+CMM vs CMM



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