Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Protocol (16th August 2007)

1. Title of the project

Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (HTA 07/08)

2. TAR team

School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield.

Lead

Mike Holmes

Operational Research Analyst

ScHARR, University of Sheffield, Regents Court, 30 Regent Street, Sheffield S1 4DA.

Direct line: 0114 2220745

Fax: 0114 2724095

m.w.holmes@shef.ac.uk

Address for correspondence

All correspondences should be sent to the project lead (Mike Holmes, m.w.holmes@shef.ac.uk).

3. Plain English Summary

Chronic pain is an important cause of physical and emotional suffering, familial and social disruptions, disability and work absenteeism. It is defined by its duration, typically greater than three months[1] beyond normal tissue healing time, and is usually less directly related to identifiable tissue damage. In addition to its duration and lack of associated pathology, chronic pain is frequently identified by an unpredictable prognosis and many associated psychological problems – particularly depression and anxiety[2] – and may include varying amounts of disability, from none to severe. Chronic pain syndromes include: chronic low back pain, fibromyalgia, neuropathic pain, phantom limb pain and central pain syndromes. Chronic pain can be continuous or intermittant.

Published estimates of the prevalence of chronic pain vary widely. Elliott et al[3] 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.

Neuropathic pain is produced by damage to, or pathological changes in the peripheral or central nervous systems. The mechanisms involved in neuropathic pain are complex and involve both peripheral and central pathophysiologic phenomenon. Ischaemic pain occurs when there is insufficient blood flow for the metabolic needs of an organ. It can be very severe and is commonly felt in the legs but it could occur anywhere. The pain of a heart attack is the prototypical example of ischaemic pain.

Spinal cord stimulation (SCS) has been used since 1967 to treat patients with intractable pain syndromes including the failed back surgery syndrome (chronic low back pain which has failed to respond to surgical treatment), and ischaemic cardiac and limb pain. The exact mechanism is unknown, but the technique may inhibit chronic pain by stimulating large diameter afferent nerve fibres in the spinal cord.

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.

SCS is not curative for the underlying condition, and may not be a stand-alone treatment but will be provided within the context of the multi-disciplinary care team. Expected benefits of SCS are reduction in pain, improved function (including general activities of daily living and also return to work), generally 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.

The aim of this review is to systematically evaluate and appraise the potential clinical and cost effectiveness of SCS for the treatment of chronic neuropathic and ischaemic pain. The outcome measures to be considered are likely to include levels of pain relief, physical activity, health-related quality of life, survival and adverse effects of treatment. The costs and cost-effectiveness will be assessed from the perspective of the NHS and Personal Social Services.

Several types of SCS devices are available in the UK. Where evidence is available an assessment will be undertaken on individual devices. Where evidence is not available then assumptions will be made on the effectiveness of the devices.

4. Decision problem

4.1 Purpose of the assessment

The assessment will address the question "What is the clinical and cost effectiveness of spinal cord stimulation in the management of chronic pain of neuropathic or ischaemic origin?"

4.2 Clear definition of the intervention

Spinal cord stimulation, also known as dorsal column stimulation, modifies the perception of neuropathic and ischaemic pain by stimulating the dorsal column of the spinal cord. 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 and to adjust the level of stimulation, within limits as prescribed by the physician. The precise mechanism of pain modulation is not fully understood but it is thought to involve direct and indirect inhibition of pain signal transmission. It is also thought that for ischaemic pain that SCS gives an additional benefit of redistributing microcirculatory blood flow.

There are two methods of pulse generation: implantable pulse generator (IPG) and 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: Advanced Bionics (Precision), Advanced Neuromodulation Systems, UK Ltd (Eon, Genesis IPG (3608), Genesis XP (3609), Genesis XP Dual (3644), Genesis G4 and Renew (3408 and 3416)) and Medtronic Ltd (Synergy, Synergy Versitrel, Itrel 3 and Restore).

4.3 Place of the intervention in the treatment pathway

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).

4.4 Relevant comparators

Medical and/or surgical treatment (appropriate to condition) that does not include spinal cord stimulation. The precise definition of the comparators will be obtained from the literature searches.

4.5 Population and relevant sub-groups

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.

4.6 Key factors to be addressed

The objectives of the review are:

- To evaluate the clinical effectiveness of SCS in terms of pain, health-related quality of life, physical and functional abilities, anxiety and depression.
- To evaluate the side-effect profile of SCS.
- 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. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

A comprehensive search will be undertaken to systematically identify clinical effectiveness literature concerning spinal cord stimulation in adults with chronic neuropathic or ischaemic pain.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

The following databases will be searched: 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 will also be searched to identify any studies not yet indexed on Medline. Current research will

be identified through searching the National Research Register (NRR), the Current Controlled Trials register and the MRC Clinical Trials Register. Sources such as Google Scholar will be searched. Table of contents from key journals will be 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 will be browsed for e.g. International Research Foundation for Complex Regional Pain Syndrome , International Neuromodulation Society, Neuromodulation Society of UK and Ireland, British Pain Society (including their guidelines on Spinal cord stimulation), European Federation of Chapters of the International Association for the Study of Pain (EFIC), 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 any relevant systematic reviews will also be hand-searched in order to identify any further clinical trials. Searches will not be restricted by language, date or publication type. The MEDLINE search strategy is presented in Appendix 1.

5.2 *Inclusion criteria*

Intervention

- spinal cord stimulator devices

This will include 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

- randomised controlled trials

Systematic reviews will not be included in the analysis, but will be checked for controlled trials that meet the inclusion criteria of this review and be retained for discussion.

5.3 *Exclusion criteria*

- Neurostimulation that involves stimulation of other parts of the nervous system (e.g. peripheral nerves, deep brain)
- Pregnant women and children
- Publications in languages other than English

Based on the above inclusion/exclusion criteria, study selection will be made by one reviewer, with involvement of a second reviewer when necessary.

5.4 *Data extraction and critical appraisal*

Data will be extracted with no blinding to authors or journal. Data will be extracted by one reviewer using a standardised form. Quality will be assessed according to criteria based on NHS CRD Report No.4 (http://www.york.ac.uk/inst/crd/report4.htm). The quality assessment form is shown in Appendix 2. The purpose of such quality assessment is to provide a narrative account of trial quality for the reader and, where meta-analysis is appropriate, inform potential exclusions from any sensitivity analysis.

5.5 *Data synthesis*

Pre-specified outcomes will be tabulated and discussed within a descriptive synthesis. Where statistical synthesis is appropriate, meta-analysis will be conducted using fixed and random effect models, using RevMan software. If sufficient trials are available, a sensitivity analysis will be undertaken to see if the removal of poor quality trials affects the results. In addition, a mixed treatment comparison using Bayesian evidence synthesis may be undertaken.

5.6 *Methods for estimating quality of life*

Any HRQoL data available from studies accepted into the review will be extracted. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model.

The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both cost and QALY will be discounted at 3.5%.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Studies relating to the costs and effects associated with SCS will be identified using an economic search filter which will be integrated into the search strategy detailed in Section 5.1; this economic search filter is presented in Appendix 1. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal[4] checklist for economic evaluations together with the Eddy checklist on mathematical models[5] (see Appendix 3).

6.2 Methods for estimating costs and cost-effectiveness

A mathematical model will be developed to estimate the cost per QALY gained for SCS. It is hoped that suitable quality of life data will be identified from the literature, in the absence of quality of life data, the model may use indirect evidence on quality of life from alternative sources. The model will use efficacy data from the key RCTs identified through the systematic searches. Cost data for the economic model will be extracted from a variety of published sources.

A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the intervention with the objective of identifying how secure the results of the economic analyses are, given the available evidence. Uncertainty with respect to model parameters will be explored with a probabilistic sensitivity analysis (PSA), where uncertainty of all input variables is modelled with probability distribution of their value. The information derived from PSA will be summarised graphically using cost effectiveness acceptability curves.

7. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 27th November 2007. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing de-novo modelling.

Any 'commercial in confidence' data taken from a company submission will be highlighted and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

All members of the advisory board have taken part in advisory groups/symposia/lectures which have been sponsored by various manufacturers for which honoraria have sometimes been received. Brian Simpson has had proposals for spinal cord stimulation electrode designs incorporated into a patent application submitted by Algotec Ltd. No payment has been received for this. Brian Simpson has in the past received a small

payment from Advanced Neuromodulation Systems for the design of an electrode for spinal cord stimulation. This product is no longer in production.

9. Appendices

Appendix 1: Draft search strategy

Strategy below to be combined with RCT, systematic review and economics filter to produce three result sets.

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$.tw.
14. peripheral vascular disease/
15. refactory angina.tw.
16. exp Brachial Plexus Neuropathies/
17. exp Radiation Injuries/
18. post-radiation.tw.
19. exp Amputation/
20. spinal surgery.tw.
21. intercostal$ 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

Appendix 2

Randomised controlled trial quality assessment scale

based on NHS CRD Report No. 4.[3]

	Yes/No/Unclear/ Not Applicable
Was the method used to assign participants to the treatment groups really random?	
What method of assignment was used?	
Was the allocation of treatment concealed?	
What method was used to conceal treatment allocation?	
Was the number of participants who were randomised stated?	
Were the eligibility criteria for study entry specified?	
Were details of baseline comparability presented?	
Was baseline comparability achieved?	
Was an intention-to-treat analysis included?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	

Appendix 3: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations[4] together with the Eddy checklist on mathematical models employed in technology assessments.[5]

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies	
3	A description of the relevant factors and outcomes;	
4	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*	
5	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;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	

9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	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;	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	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;	
13	A description of research in progress that could yield new data that could alter the results of the analysis	

[1] International Association for the Study of Pain., Classification of chronic pain, Pain (1986) (suppl 3), pp. S1-S226.

[2] Ashburn MA, Staats PS. Management of chronic pain. Lancet 1999; 353(9167):1865-1869.

[3] Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet 1999; 354(9186):1248-1252.

[3] NHS Centre for reviews and Dissemination. *Report 4: Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews*. York: University of York; 2001.

[4] Drummond, M and Jefferson, TO Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; **313** 275-283.

[5] Eddy, DM *The role of mathematical modeling. in Assessing medical technology. Technology Assessment* 1985;144-154.