# Neuromodulation Society UK and Ireland

## Comments on the NICE Appraisal Consultation Document

General Comments:

i) Do you consider that all of the relevant evidence has been taken into account?

1. CRPS

The Appraisal Consultation Document (ACD) has taken into account the evidence from the RCTs examined by the HTA conducted by the SCHARR group. It does not take into account the detailed new and full publication by Kemler et al (JNeurosurg108:292–298, 2008). The ACD also comments on the uncertainty of the effects of SCS on CRPS in the long term but fails to take into consideration numerous longterm follow up case series on the subject such as the 101 case series by Bennett D, Alo K, Oakley J, et al. Spinal cord stimulation for complex regional pain syndrome I (rsd). Neuromodulation. 1999; 2:202–210. While case series type publications are open to a number of biases in the absence of any long term follow up RCTs of a large group of patients they will provide valuable data.

While the ACD acknowledges that both FBSS and CRPS are neuropathic pain conditions and recommends SCS for FBSS, it fails to address SCS in other causes of neuropathic pain where a large number of case series show efficacy for SCS in this group of patients where 50% are refractory to drug therapy (EFNS guidelines on pharmacological treatment of neuropathic pain Attal et al. European Journal of Neurology 2006, 13: 1153–1169). As a group of physicians with long expertise in the use SCS we feel that this particular group of patients will be particularly disadvantaged by the current ACD recommendations. While no RCT exists for this group of patients a lack of RCTs does not equate to a lack of effectiveness and the literature on SCS should be considered as a body rather than RCTs in isolation.

2. CLI

The study conducted by Amann, W. Spinal cord stimulation in the treatment of nonreconstructable stable critical leg ischaemia: results of the European Peripheral Vascular Disease Outcome Study (SCS-EPOS). European Journal of Vascular & Endovascular Surgery 2003; 26 280-286). Is alluded to briefly both in the ACD and the HTA. The study is not an RCT but explores adequate selection criteria for candidates for SCS in CLI.

The study shows clearly that the SCS group with selection criteria applied (SCS match group) has better limb survival than patients with SCS and no selection criteria or patients with no SCS. The paper was not analyzed in the HTA as it is not an RCT. It has been alluded to in the HTA document .

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?

1. CRPS

The summaries of cost effectiveness on CRPS is a skewed interpretation of the literature. This is based largely on the fact that the 5-year analysis of SCS+PT vs. PT alone had not been published fully by Kemler (JNeurosurg 108:292–298, 2008) We have a number of comments relating to this study

a) The ACD acknowledges that the study was a small study (54 patients) with a large crossover 4/18 patients of the PT group received an SCS implant and 12/36 in the SCS group did not receive an SCS because of failed test stimulation. Under those conditions the groups at 5 years where no longer representative of the groups

b) Kemler does not conduct an ITT analysis of the original randomized groups but chooses to exclude some of the randomized patients (4 in the PT group because of SCS implant and 1 in the SCS+PT Group because of a special implant). This is no longer a conventional ITT analysis but is taken as such without question in the ACD document.

c) In the ACD, the committee concludes that there is considerable uncertainty regarding the long term effects of SCS in CRPS but takes little account of the fact that in the Kemler study at 5 years. Among patients (90%) of 20 patients with an SCS indicated that they had positively responded to the treatment, and 19 patients (95%) reported that they would undergo the treatment again for the same result.

d) The same study conducted an unconventional per treatment analysis, which excluded 4 patients who were randomized to PT but actually received a stimulator and one patient in the stimulator group who received a special SCS implant. This per treatment analysis shows a continued effectiveness of SCS at 5 years.

e) The Kemler study population had suffered with CRPS for an average of more than 3 years at baseline. The patients had an average baseline VAS score of 7. This is a high score when 5.4 is considered as severe and the committee is recommending SCS for patients with VAS scores above 5 in FBSS

f) The committee concludes that SCS is cost effective at IPG life longer than 4 years. It is important to note that the technology used by Kemler et al is now outdated. In our experience this would have a profound effect on battery life as well as the number of SCS trail failures

In the economic analysis for the CRPS group of patients different ICERs are arrived at in the ABHI submission vs. the SCHARR HTA analysis. This is dependent on the estimation of the baseline utilities value for that group of patients. In the ABHI submission a similar group of patients (FBSS patients with severe pain) derived from the PROCESS trial (an RCT) are used. THE SCHARR HTA group derived the baseline utilities value from the Mc Dermott et al paper

(Mc Dermott et al. European Journal of Pain 10 (2006) 127–135). This is not an RCT but a cross sectional observational survey. Furthermore the Mc Dermott group of patients is far from representative of patients with severe CRPS seen in a hospital setting as the patients are sampled from GP surgeries. As a matter of fact the authors comment on their sample choice " We limited sampling to non-pain specialists in order to evaluate a broad range of neuropathic pain severity, including patients with milder forms that may not have been evaluated by a specialist". The utilities for this group, even the severe pain range, will clearly not represent the severe pain CRPS patients for which SCS is clinically appropriate.

International Guidelines for the treatment of CRPS developed under the auspices of the International Association for the Study of Pain (IASP), recommends SCS for CRPS at 12-16 weeks. This guideline was developed by a panel of internationally recognized experts in the care of CRPS patients (Stanton-Hicks M. et al .An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. Pain Pract. 2002;2(1):1-16). The Kemler study population had suffered with CRPS on average for more than three years.

SCS should be recommended severe CRPS where conventional medical management has failed to achieve a result or facilitate physiotherapy

Refractory Angina:
1. In The ESBY study SCS vs. CABG, the SCS group show a similar effectiveness to the CABG group at 5 years and a non significant tendency towards improved survival. The HTA concludes that SCS dominates CABG. The committee considers that as this group of patients could undergo CABG they are not true RA patients and therefore the study is unrepresentative of the patient group.
2. In the SPiRiT trial SCS was shown to be as effective as PMR in patients regarded as being truly RA. The patients receiving SCS were drawn from all over the UK and had poor follow up arrangements for reprogramming. The trial design insisted upon using an outmoded electrode technique for stimulation.
Both the studies show that SCS is equivalent to the gold standard in Angina and Refractory Angina patients. Murray et al "Spinal cord stimulation significantly decreases the need for acute hospital admission for chest pain in patients with refractory angina pectoris" Heart 1999;82:89-92 a UK study of costs before and after SCS in 19 consecutive patients provides UK data of cost benefit. This is in an RA population. Cost savings are due to the fall in annual admission rates.
In light of the above evidence SCS should be available to patients who are suitable for CABG but are unable to undergo the procedure because of high clinical risk. As well those who are unsuitable for reoperation. (True RA)
In the UK clinical context SCS is only considered as an option following referral from a cardiology team consideration of other pain management techniques as per the Guidelines created by the Cheshire and Merseyside Cardiac Network on "Diagnosis and Management of Stable Angina" can be found at the link below – http://www.cmcn.nhs.uk/guidelines/stable_angina.html

Critical Limb Ischaemia:

The study conducted by Amann, W. Spinal cord stimulation in the treatment of nonreconstructable stable critical leg ischaemia: results of the European Peripheral Vascular Disease Outcome Study (SCS-EPOS). European Journal of Vascular & Endovascular Surgery 2003; 26 280-286). Is alluded to briefly both in the ACD and the HTA. The study is not an RCT but explores the effects of adequate selection criteria on candidates for SCS in CLI.

In our experience the number of candidates with CLI who would be inappropriate for reconstructive surgery and would match the Amann selection criteria represents a small subgroup of CLI sufferers as a whole.

The study shows clearly that the SCS group with selection criteria applied (SCS match group) has better limb survival than patients with SCS and no selection criteria or patients with no SCS. The paper was not analyzed in the HTA as it is not an RCT. However in issuing guidance to the NHS the committee should consider in full the clinical implications of the results of the study on a small group of patients who would otherwise go on to loose their limbs as a result of guidance restricting the use of SCS to research.

Burger' s disease also represents a small subgroup of young patients where an RCT does not exist but clinical experience confirms effectiveness of SCS. Condemning this group to an assured amputation in their 3rd decade would not constitute sound clinical guidance

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

FBSS:

On the subject of FBSS the ACD provides sound guidance in line with the evidence, the recommendation however should be broadened to include SCS for other clear aetiologies of neuropathic pain that have not responded to conventional medical management, as the ACD document agrees that both FBSS and CRPS are neuropathic pain conditions. Clinical effectiveness has been demonstrated for both conditions, which are taken to represent a wider spectrum of neuropathic pain conditions. On the subject of the necessity of a trial of spinal cord stimulation prior to implant. The ACD recommends that a trial must be carried out as in the studies. Clinical practice differs from randomized studies and as there is no evidence that a trial of SCS improves outcome, a trial should be recommended but not be a mandatory requirement. Payers may well interpret the guidance as mandating a trial in every patient. This can be counterproductive in the immunocompromised patient.

CRPS:

On the subject of CRPS the guidance provided is unfortunately a poor conclusion based on misinterpretation of the evidence and poor reading of the 5 year Kemler study as well as poor choice of sample for baseline utilities . The guidance as it

stands would disadvantage a group of patients who have very little in the way of treatment options. SCS and other pain relieving methods are employed in CRPS to enable physiotherapy. In case of failure of other interventions (as outlined in the international guidelines) SCS should be recommended in this group of patients in line with the available evidence and international guidelines. In our experience as a group of clinical experts CRPS patients respond well to early intervention with SCS. Also their battery life with current technology far exceeds the 4 years quoted by the research using outdated SCS models.

Angina:
The evidence quoted has shown SCS to be equivalent to the current gold standard for the treatment of angina i.e CABG. SCS is also equivalent to PMR (Percutaneous myocardial revascularization) the ACD states" All four trials recruited people with RA for whom revascularisation procedures were unsuitable or for whom it was considered that revascularisation would not improve prognosis" (4.1.9) The committee however proceeds with a different interpretation of the evidence based on the groups of patients recruited for the trial. We have used SCS in angina for more than 15 years have found it to be an effective treatment in line with the evidence from the studies.. We find the committee's recommendations on this subject difficult to comprehend in a group of patients who, in our experience respond extremely well and rarely require battery replacements. We find that RA is one of the best indications for SCS. SCS should remain an option for RA and Angina with significant co-morbidity. SCS should be available to those that manage patients with Refractory angina in a multidisciplinary setting with clear clinical pathways.
Multidisciplinary pain management has been shown by NRAC to achieve best results.
CLI:
The ACD alludes to the Amman study but makes no comment on it. We feel that the guidance as it stands would disadvantage the group of patients who match the Amann study selection criteria and who again in our experience benefit significantly from SCS Another group that would be tragically disadvantaged from this guidance would be patients with Buerger's disease and vasospastic disorders, who again, in our clinical experience respond extremely well to SCS. It is clear that the therapy makes a huge impact on the Quality of life of this group of patients.

ON CLI as well the other indications we feel that the restrictions imposed by the HTA in considering only RCTs should be lifted at this stage and the committee should be considering a larger body of evidence including case series and non randomized trials.

Implementation:

Implementation

SCS as a therapy area has survived in the UK due to the interest of clinicians from functional neurosurgery and pain anaesthesia. There are approximately 30 implanting centres within the UK. A few perform up to 60 new patient procedures per year and some less than 10.

Clinical networks:

Best practice with SCS is achieved where SCS is carried out in high volume centres within the context of a multidisciplinary team. It will be essential to develop care pathways in order to support successful commissioning. Existing centres will need to expand; it's possible that a few other centres will need to be established

Clinical Training:

There is a deficit in training facilities for SCS. NSUKI, St Thomas's, Walton centre and the industry partners provide training. A few receive limited training as part of their CCST.

The Faculty of pain medicine is responsible for over seeing SCS training for anaesthetists within the arrangements for specialist training of anaesthetists in pain medicine. SBNS is responsible for neurosurgical training.

Device registration, audit, governance and research

Throughout the appraisal process we have mentioned the need for device registration, clinical audit and governance and a coordinated approach to future research. The professional societies believe there is a good case for a web-based registry to capture all implant activity throughout the UK. NSUKI is currently running a pilot national registry for pain implant devices. This effort is coordinated by Dr Simon Thomson.

Specific comments on the ACD document:

1.1 Should be changed to express clearly that a trial stimulation is desirable but not mandatory and that in line with the evidence from PROCESS and North study this group of patients should not have to exhaust all avenues of standard care before they are considered for SCS

1.2 The recommendations for SCS in CRPS, RA and CLI should be revised in line with the evidence presented by the HTA, other evidence as case series and non randomized trials etc.. See general comments above

1.4 & 4.3.3. Trials should be desirable but not mandatory especially in the immunocompromised group.

2.4 The term pain management program is used in error in this context. A Pain Management Program (in the context of chronic pain management) implies a specific cognitive behavioral group therapy. We believe the term" multidisciplinary approach" would serve the meaning better and allay any confusion.

4.1.10 RA patients find pain ratings very difficult to express as their pain is usually described as severe and intermittent. Use of Nitrates hospital admissions and frequency of angina attacks are better clinical indicators

4.2.7 An annual withdrawal rate of 3.24% per annum, is assumed to be because of gradual loss of pain control for the SCS group in the model. No withdrawal rate is assumed to occur for the CMM group in both models this does not reflect clinical reality as tolerance to drugs, injection techniques and psychological and physical rehab techniques are well documented. Why was no withdrawal rate assumed for CMM? Why are no complications assumed in the CMM group? This again bears no resemblance to clinical reality.
4.2.9 The cross sectional survey of McDermott et al is not representative of patients with severe CRPS who would be candidate for SCS implant, even the severe pain group. Both the HTA and the ACD are mistaken on this assumption. While the patients included CRPS patients they were recruited from GP surgeries, which is by definition a different population from the hospital CRPS population. Why was this survey (not RCT) allowed? And how can it be safely assumed that these patients represent the refractory group of CRPS patients referred for SCS?
4.2.13 If device longevity becomes the deciding factor in the ICER, a trial of SCS would help the clinician decide on estimated device longevity based on the current usage during the trial. CPRPS patients with a successful trial and low current requirements should be allowed to proceed with a final implant
4.3.5 The Committee therefore recognizes that price and longevity were not independent and that longevity varies depending on an individual's pain characteristics. Does the committee realize that some devices allow the clinician to estimate device longevity based on trial data?
4.3.6 The committee's conclusions on its specific guidance would disadvantage a group of patients with rare causes of neuropathic pain for whom an RCT will never be possible as FBSS and CRPS  are both neuropathic pain conditions. The final guidance should therefore recommend SCS for severe neuropathic pain of clear aetiology that has not responded to CMM.
4.3.7 Neither the committee nor the experts had access to the Kemler 5 year full data. The comments above on the conduct of the ITT in this paper lead to different conclusions nevertheless the committee's conclusions on long term results of CRPS are bizarre given the comments from the experts.
4.3.8 Pain outcomes are difficult for RA patients to rate as their pain is intermittent and severe, in CLI pain ratings are very different at rest from on movement hence patients have great difficulty in providing pain ratings
4.3.9 Reduction in the effects of the comparator are not taken into account by the committee. The rare but serious complications of SCS are overemphasized as they relate mainly to surgical lead implant and are no different from complications of a laminectomy pr ocedure (standard practice in the NHS)
4.3.11 accurate utility data for CRPS is now available
4.3.12 from a clinical perspective RA patients are the best indication for SCS we therefore find the committee's interpretation of the available evidence at odds with the clinical reality. As the RA population respond to implant with simple devices have low current requirements and rarely require battery replacement. The interpretation of the data should not hinge entirely on the question of refractoriness of the population in the studies

On behalf of NSUKI

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