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4th July 2008

Dear Ms Saile,

Re: Appraisal Consultation Document (ACD) on Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin

Thank you for the opportunity to respond to the ACD for this technology appraisal. After thorough review of the ACD and the associated Evaluation Report (ER), on behalf of the cross industry group, we would like to draw your attention to a number particular issues that we believe either have not been given due consideration further to our Assessment Report (AR) comments submitted to the Institute or do not constitute fair guidance in view of the evidence considered by the appraisal committee. These comments will be addressed under three main headings:

1. Clinical and cost-effectiveness of complex regional pain syndrome (CRPS)
2. Clinical and cost-effectiveness of refractory angina (RA)
3. RCT data inclusion for peripheral vascular disease and relevant population identification (PVD)

1. Clinical and cost-effectiveness of complex regional pain syndrome (CRPS)

In section 1.2 of the ACD it states that "Spinal cord stimulation is not recommended as a treatment option for adults with complex regional pain syndrome…..except in the context of research as part of a clinical trial".

The rationale behind this recommendation appears to be primarily due to the Assessment Report's base case ICER of >£30,000/QALY which persuaded the committee that the use of SCS for the treatment of CRPS could currently not be considered as a cost-effective use of NHS resources. This opinion, combined with a concern that serious adverse events (SAEs) were not incorporated in the model and that 5 year follow-up data from the Kemler trial does not show a sustained difference

between SCS and CMM has, we believe, wrongly led the committee to issue inappropriate draft guidance to the NHS on the use of SCS for CRPS.

To help inform the committee's next discussions, we have conducted some re-modelling using the AR acquisition cost for SCS and appropriate CRPS specific utilities, analysed SAEs reported in clinical trials and assessed the validity of the 5 year Kemler data.

1.1 CRPS Re-modelling

Despite our request to NICE, access to the ScHARR model was not made available. The reanalysis was therefore undertaken using the ABHI model. However, as outlined in the Overview (Section 3.2.3) the ScHARR economic model was based on the ABHI model and from the description from the ScHARR assessment report, the structure of the two models appeared identical.

Two inputs to ABHI CRPS model were updated:

a. Device cost
The ABHI model device cost was updated to £9,000 as outlined in the NICE ACD (Section 4.2.8).

b. Health state utility
We acknowledge the comment in section 4.3.11 of the ACD i.e. "The committee noted that the models used different sources of utility data and that neither captured the utility of a person with CRPS accurately, as one source was a trial of FBSS [ABHI model] and the other a wider survey of neuropathic pain conditions [ScHARR model]." The ScHARR ICER for CRPS is based on a survey of utility values by McDermott et al sourced from neuropathic patients none of whom has CRPS. We contend this ICER is therefore invalid.

To overcome the limitation of previous ABHI model analysis we obtained individual patient EQ-5D data that was collected within the Kemler trial of SCS for CRPS trial (data on file). This data is the best quality utility data available for the patient group of interest and could be correlated with the health states. In accord with the FBSS cost effectiveness analysis, it was assumed that the pre-defined health states of pain relief were independent of type of treatment mechanism (i.e. how that pain relief was achieved). The proportion of patients in each health state in the first 6-months was based on the 6-month findings from the Kemler trial. The health state values are summarised in the table below.

Table 1. Utility values for CRPS health states

Pain threshold	Health state (6 month findings from Kemler)	Utility
≥50%	Optimal pain relief	0.61
≥50%	Optimal pain relief + Complication	0.56
<50%	Sub optimal pain relief	0.23
<50%	Sub optimal pain relief + Complication	0.18
0%	SCS to CMM failure (no perceived pain reduction): assumed to be equivalent to baseline	0.16

Over the 15-year time horizon of the model, the following base case cost effectiveness results were obtained:

Table 2. Base case cost effectiveness of SCS and CRPS

CRPS	SCS + CMM	vs	CMM alone		Difference
Total cost	£92,519		£81,088		£11,431
QALYs	6.07		5.35		0.71
Cost /QALY			**£16,088**		

SCS produced more QALYs (0.71 per person) for relatively little extra cost (£11,431) compared to CMM, the equivalent of a cost per QALY (ICER) of £16,088. This ICER falls well below the ICER of £32,282/QALY as stated in the ACD section 4.3.11 (which is in conflict with the base case value stated in the AR and ER of £25K) and below the threshold of £20,000/QALY.

In probabilistic sensitivity analysis it was found that SCS was over 70% cost-effective at the £30,000 per QALY threshold; the probability of being cost effective at £20,000 per QALY was over 50%. The scatter plot and CEAC produced from probabilistic analysis are shown below.

Figure 1. Scatter plot of incremental QALYs and costs for SCS and CRPS

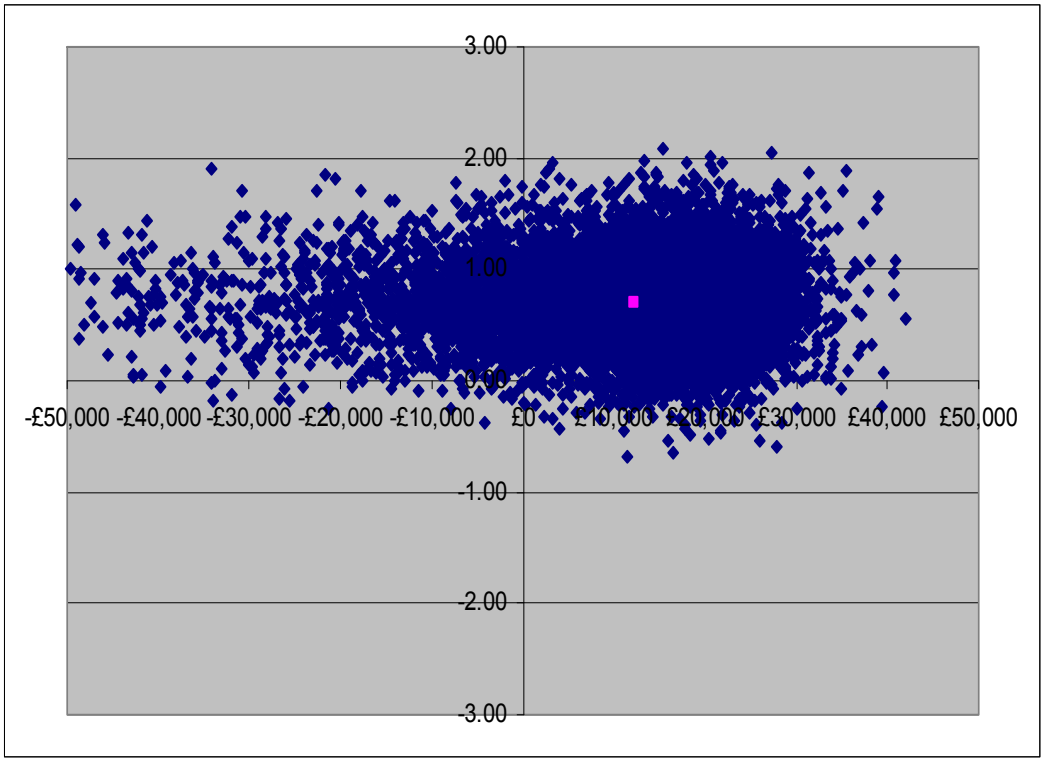
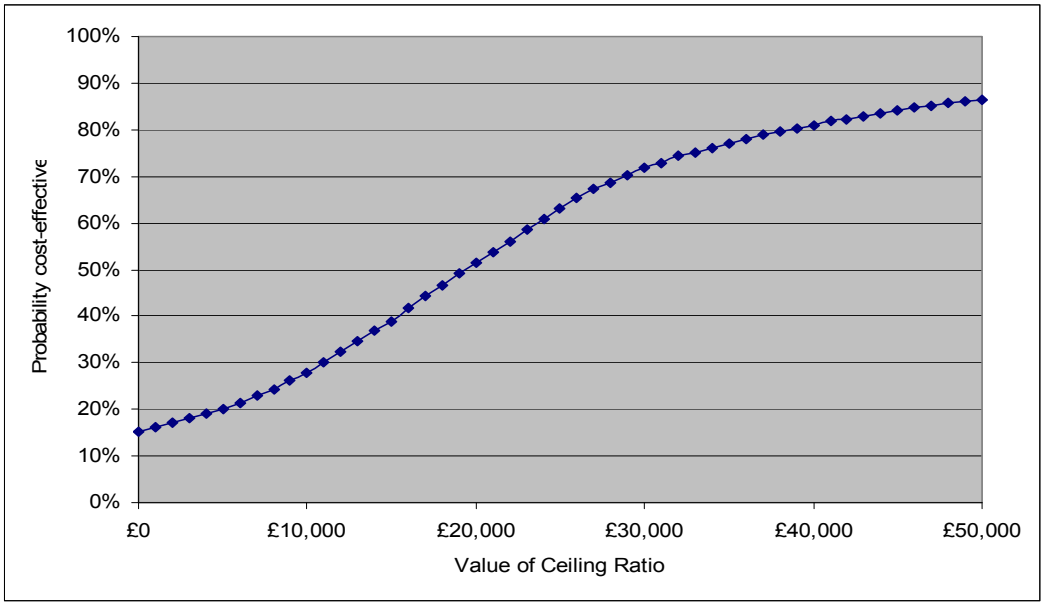


Figure 2. Cost effectiveness acceptability curve for SCS and CRPS



In summary, the ScHARR ICER for CRPS stated in the ACD is based on a survey of utility values sourced from neuropathic patients none of whom has CRPS. Although this was the best data available at the time, due to the new availability of CRPS specific utilities we believe the ScHARR ICER to be invalid. A reanalysis of the cost effectiveness of SCS for CRPS was undertaken using the ABHI model and health state utility values directly sourced from EQ-5D data collected from CRPS patients in the Kemler RCT of SCS. In this reanalysis the device cost was updated to £9,000 as stated in the ACD. Our reanalysis clearly demonstrates SCS+CMM to be a cost effective compared to CMM for CRPS with an ICER of below the threshold of £20,000/QALY. On the basis of these results, and in accord with FBSS, SCS should be recommended as a treatment option for adults with CRPS who continue to experience chronic pain (measuring at least 50 mm on a 0–100 mm visual analogue scale) for at least 6 months after surgery despite adequate standard care, and who have had a successful trial of SCS stimulation.

1.2 Trial reported SAEs

It states in the ACD that the Committee noted that rare, but potentially serious, complications were not included in the model and as a consequence it is possible the model may underestimate the ICER for SCS. We refute this assertion and provide trial data to show that SAEs are not relevant to the modelling. The clinical trial reports from 9 studies run in Europe since 1995, involving 443 patients (with adverse events reporting and monitoring) reported no deaths, comas or paralyses (please see attached table). We therefore believe that non inclusion of SAEs is an accurate and clinically relevant approach and that it has not caused the ICER to be underestimated. With respect to all adverse events, none are included for CMM in the model, therefore we believe the ICER to be conservative for SCS.

1.3 Validity of the 5 year Kemler data

Unlike the six month ITT Kemler utility data used in the revised economic model, we believe that the five year data discussed by the committee has been interpreted inappropriately to conclude that there is uncertainty surrounding the long-term advantages of SCS. This is despite the committee hearing from clinical specialists that this may have been partly explained by crossover between the treatment arms of the trial. There a number of reasons why the five year Kemler data is unsuitable for determining five year relative effectiveness of CMM and SCS, these are detailed below.

a. Background on Kemler study: previously reported six- and 24-month results

Patients selected for the Kemler study were enrolled between March of 1997 and July of 1998 and were randomized 2:1 to either SCS plus physical therapy (SCS+PT) (n = 36) or PT alone (n = 18). Of the 36 patients randomized to SCS+PT, 24 (67%) were implanted.

At six months, in an intention-to-treat (ITT) analysis, the mean VAS score for SCS+PT patients decreased by 2.4 cm, while it increased by 0.2 cm for PT-only patients ($p < 0.001$). In an as treated analysis, the mean VAS score for SCS+PT implanted patients decreased by 3.6 cm, while it increased by 0.2 cm for PT-only patients ($p < 0.001$). In the as-treated analysis, global perceived effect (GPE) was much improved in 14 (58%) of the 24 SCS+PT implanted patients, as compared to one of the 18 (6%) PT-only patients ($p < 0.001$). SCS+PT also resulted in significant improvements in health-related quality of life (HRQoL) both for patients with an affected hand ($p = 0.02$) or foot ($p = 0.008$).

At the two-year follow-up, in an ITT analysis, mean pain intensity (VAS) decreased by 2.1 cm for SCS+PT patients compared to 0 cm for PT-only patients ($p < 0.001$). In the as-treated analysis, mean VAS score decreased by 3.0 cm for SCS+PT implanted patients compared to 0 cm for PT-only patients ($p < 0.001$). In the as-treated analysis, GPE was much improved in 15 of the 24 (63%) SCS+PT implanted patients, as compared to 1 of 11 (9%) PT-only patients ($p < 0.001$). HRQoL benefits remained the same.

b. Kemler study for CRPS: five-year results

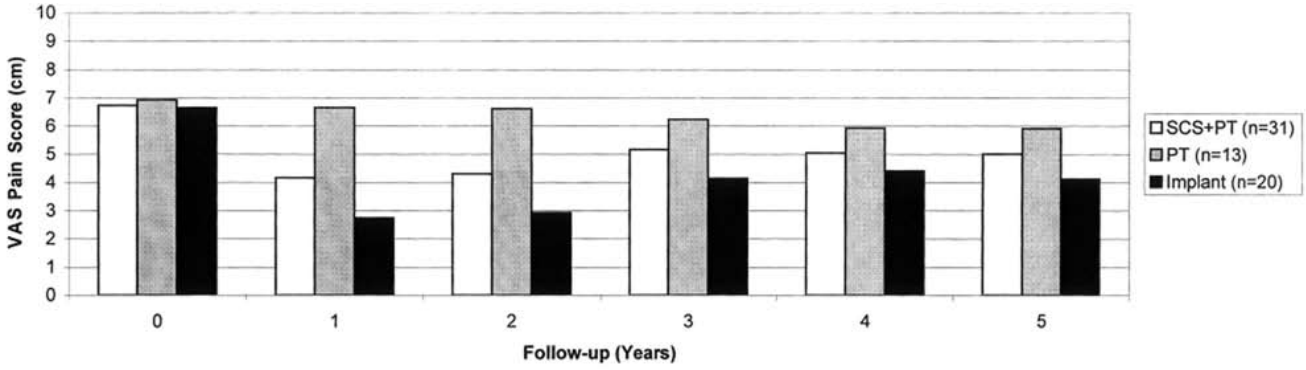
After five years, in the main analysis the mean pain intensity for the patients randomized to SCS+PT (n = 31) was reduced by 1.7 cm versus 1.0 cm for the patient randomized to PT only (n = 13) ($p = 0.25$). Twenty-three percent (23%) of the SCS+PT patients reported much improvement on the GPE scale, while 15% of PT-only patients reported much improvement ($p = 0.24$). HRQoL changes were not statistically different between groups.

In the subgroup analysis of permanently implanted patients (n = 20) versus PT-only patients (n = 13), the average pain relief (VAS) was 2.5 cm compared to 1.0 cm ($p = 0.06$). Thirty-five percent (35%) of the SCS+PT implanted patients reported much improvement on the GPE scale, while 15% of PT-only patients reported much improvement ($p = 0.02$). HRQoL measures were not significantly different between groups. Patient satisfaction in SCS implanted patients was also very high. After five years, 90% of SCS implanted patients indicated that they had positively responded to SCS, and 95% reported that they would undergo treatment again for the same result.

c. Pain scores at five years are moderate for SCS-implanted patients and severe for PT-only patients

In the as-treated analysis of SCS+PT implanted patients versus PT-only patients, the difference in VAS pain score change approached statistical significance (p = 0.06) in favor of SCS and that difference was likely to be clinically meaningful to patients. As Figure 1 demonstrates, the mean VAS score for SCS implanted patients was relatively steady over years 3-5 and was still nearly two points lower than PT-only patients at year five. Furthermore, the average VAS score for SCS implanted patients was in the range of scores considered to equate to moderate pain, while the average score for PT-only patients was in the range of scores considered to equate to severe pain.

Figure 1: Bar graph demonstrating the mean (± SD) VAS pain scores in patients with complex CRPS-I. The groups in the main analysis are represented by white and grey bars, whereas the subgroup of patients with an implant at the final follow-up is represented by black bars.



d. The nature of the analysis was unconventional

Kemler's main analysis should have employed ITT analysis whereby comparisons would be made between the patients randomized to SCS+PT versus the patients randomized to PT only, regardless of what actually happened with their treatment. In fact, Kemler excludes one SCS+PT randomized patient due to a special implant and excludes four PT-only randomized patients due to SCS implant. ITT analysis is valuable because it allows the balance of known and unknown patients' characteristics to remain equal between the two treatment groups as a result of randomisation. As ITT was not employed, we cannot be sure that the two treatment groups are directly comparable or if selection bias exists.

Kemler's subgroup analysis should have employed an as-treated approach whereby comparisons would be made between all patients who actually received an SCS implant (n = 27) versus all patients receiving PT only (n = 22). In fact, Kemler excludes one SCS+PT randomized patient who received a special implant, four PT-only randomized patients who received an SCS implant, and nine SCS+PT randomized patients who received PT only due to a failed SCS trial. As-treated analysis allows you to analyze the patients based upon the treatment they actually received. In the case of this study, as-treated analysis offers value because several patients randomized to SCS

never received the therapy and several patients randomized to PT-only received stimulation.

The use of a post-randomisation baseline pain measure raises concern. As the study was not blinded, the patients' perceived baseline pain intensity may have been influenced by knowing which treatment they were about to receive. Analyzing five-year outcomes versus baseline values may no longer be a valid comparison for two reasons. First, patients may reframe their pain, meaning that the patient considers his or her pain experience from a new reference point. Treatment may allow them to increase their level of functioning. This enhanced level of activity might then become their new normal. As they push their bodies to do more, they may perceive their pain as being worse, when in fact they are performing an activity that previously was difficult or impossible due to pain. Secondly, their disease may have progressed or changed over time to involve additional painful regions or different painful regions.

e. CRPS symptoms are heterogeneous and dynamic

The character of CRPS pain evolves over time, and in 10% of patients spreads to a new region or limb. As Kemler notes, the pain may, on occasion, even resolve. Whether programming was adjusted to treat the changing nature of the patients' pain in Kemler's study is unknown. Further, the ability to adjust programming was limited for patients with the Itrel 3 and quadripolar leads compared to the systems and software available today. Significant differences in pain relief and the ability to recapture pain relief without reintervention have been reported in retrospective analysis for patients with dual lead octapolar systems versus single lead quadripolar systems.

2. Clinical and cost-effectiveness of refractory angina (RA)

Section 1.2 of the ACD states that "SCS is not recommended as a treatment option for patients with….. refractory angina except in the context of research as part of a clinical trial". We do not believe that this recommendation is in line with the results of the available evidence base.

From analysis of the committee's deliberations it is clear that their current preliminary recommendation is based on the facts that:

a. The primary outcomes in these studies were functional rather than pain relief, and noted that no studies had demonstrated statistically significant differences for pain outcomes, hence there was considerable uncertainty about the benefits of SCS in people with RA.

b. There is no definitive economic analysis on SCS in the RA population: i.e. economic analyses provided were based on a population of people for whom treatment with CABG or PCI was suitable, however these techniques are often unsuitable for people with RA.

Whilst we concur that the evidence base for RA is less mature than that available for FBSS and CRPS, we still believe there to be enough high quality evidence available to recommend SCS in some RA patients.

It is important to consider that both the ESBY and SPIRIT trials showed non-inferiority of SCS vs. CABG and PMR respectively.

The ESBY trial is critiqued for using CABG as the comparator. Whilst we agree that CABG is not standard treatment for RA it is important to note that CABG is known to be a highly effective treatment option in the severe angina population. Consequently, the fact that both SCS and CABG offered long lasting improvements in QoL and that the survival up to 5 years was comparable between the two groups should not be disregarded and be considered to cast "uncertainty" over the effectiveness of SCS in angina. The clinical benefits of SCS in this population also translate into economic benefits as reported by Andrell et al. in 2003. In an analysis of the 2 year follow-up data of the 104 patients in the ESBY trial it was found that "SCS proved to be a less expensive treatment modality in angina pectoris than CABG ($p < 0.01$). The SCS group had fewer hospitalisation days than CABG ($p < 0.0001$) and fewer days related to cardiac events ($p < 0.05$)…. There were also no serious complications related to the SCS treatment". We believe this to be strong supporting data in favour of the use of SCS in the angina population; non-inferiority and economic benefit despite going head to head with a challenging comparator should not be overlooked or its importance underestimated.

In addition to the ESBY trial data, the results of the SPIRIT trial were considered. The SPIRIT trial is a UK open label, single centre, parallel group randomised trial conducted in a tertiary referral centre comparing percutaneous myocardial laser revascularisation (PMR) with SCS in patients with RA i.e. the correct, and UK specific population is being evaluated. The aim of both PMR and SCS is to relieve the disabling symptoms of RA. In the AR it is acknowledged that the design of the SPIRIT trial is robust. The method of randomisation was reported and adequate and whilst SPIRIT did not present ITT, the authors 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. The power calculation (for primary outcome measure) was reported and sufficient patients randomised in the SPIRIT trial.

The primary outcome of the SPIRIT trial assessed .angina functional outcomes. The SPIRIT trial assessed change in angina class as measured by the Canadian Cardiovascular Society (CCS) angina scale. Whilst at baseline all patients were in CCS class 3 or 4, 68% of PMR and 61% were in class 3 (p 0.781). At one year more SCS patients were in CCS class 1 or 2 and the difference was marginally significant at the traditional level (p 0.059). Four PMR patients had a 2-class improvement in CCS compared to 9 SCS patients who had a 2-class and 2 who had a 3-class improvement. Again, the greater proportion with a significant improvement in CCS class in the SCS group was close to traditional levels (p 0.068). The difference 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 ($p=0.042$).

Whilst further research would strengthen the existing evidence base, it should not stop the use of SCS in RA outside of an RA study or trial. The optimal RA population should be discussed at the next committee meeting. It is as important to consider functional outcomes as pain outcomes. This corroborates the criticism we have with assessing angina in terms of purely pain symptoms as opposed to functional outcomes.

3. RCT data inclusion for peripheral vascular disease and relevant population identification (PVD)

We would like to reiterate our statement from our review of the AR with respect to PVD. We fully understand that the decision of what PVD population will benefit most from treatment with SCS is problematic. We believe that the clinical review is comprehensive, however, the Cochrane review of SCS and PVD has still not been considered due to the selection criteria applied. We would advise consideration of this Cochrane review as it is a high quality systematic review of the literature PVD clinical literature: "Patients suffering from inoperable critical leg ischemia (CLI) ultimately face a major amputation". Spinal cord stimulation (SCS) has been introduced as a possible treatment option. This paper presents the best available evidence from a systematic review on the effectiveness of SCS in these patients and discusses the indications for SCS therapy. A meta-analysis of six controlled trials, including 444 patients, showed 11% (95% confidence interval: _0.02 to _0.20) lower amputation rate after 12 months compared to those treated with optimum medical treatment. In addition, SCS patients required significantly fewer analgesics and showed a significant clinical improvement. These positive effects have to be weighed against the higher costs and (generally minor) complications of SCS. TcpO2 measurements were found to be useful in selecting the most respondent patients, yielding a 12-month limb salvage of up to 83%. Hence, SCS should be considered as a possible treatment option in patients with CLI, particularly if their foot TcpO2 is between 10 and 30 mmHg." (J Pain Symptom Manage 2006;31:S30--S35. _ 2006) This Cochrane review, based on 6 well performed trials with 450 patients in total, concluded that the amputation free interval after 1 y was significantly lower in the SCS-patient group.

We believe that the Cochrane review results should be given due consideration in determining the relevant population relevant for SCS in this guidance.

Summary:

CRPS is a cost-effective treatment for use in the NHS
Due to the new availability of CRPS specific utilities we believe the ScHARR ICER to be invalid. A reanalysis using CRPS specific 6 month utilities sourced from Kemler and a device cost of £9,000 clearly demonstrates SCS+CMM to be a cost effective compared to CMM for CRPS with an ICER of below the threshold of £20,000/QALY.

No SAEs forum in clinical trial reports
Non inclusion of SAEs in the economic model is an accurate and clinically relevant approach that has not caused the ICER to be underestimated.

Five year Kemler data is unsuitable for determining long-term relative effectiveness of CMM and SCS
Due to a number of reasons detailed above, the committee has misinterpreted the data to conclude that there is uncertainty surrounding the long-term advantages of SCS in CRPS.

There is enough high quality evidence available to recommend SCS in some RA patients

The results of the ESBY and SPIRIT trials need to be reassessed. It is important to consider that both the ESBY and SPIRIT trials showed non-inferiority of SCS vs. CABG and PMR respectively.

RCT data inclusion for peripheral vascular disease readily identifies the relevant population for the indication
We believe that the Cochrane review results should be given due consideration in determining the relevant PVD population suitable for SCS treatment in this guidance.

Thank you again fro the opportunity to comment on the ACD. If you have any questions or need any further clarification, please do not hesitate to contact me.

Yours sincerely,

[redacted], UK Market Affairs