FPM
Faculty of Pain Medicine
ANZCA

9 March 2023

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Sent via email: c/o Payel Patal Payal.Patel@health.gov.au

Dear Penny,

## FPM submission to post-listing review of spinal neuromodulation devices (SNMDS)

**Preamble**

The Faculty of Pain Medicine (FPM) of the Australian and New Zealand College of Anaesthetists (ANZCA) is the professional body responsible for training and setting standards of practice in pain medicine, a specialty which is unique to this jurisdiction. FPM is a bi-national organization characterized by an interdisciplinary approach to the management of pain. It was established as part of ANZCA in 1998, and has been recognized within the international pain community as a leader in education, training, governance and professional standards.

**Responses to questions in the Review**

1. **The post-listing review is considering spinal cord stimulators, which treat chronic pain by delivering electrical impulses via leads placed in the epidural space. The following devices are outside the scope of this review: peripheral nerve stimulators, sacral nerve stimulators and vagal nerve stimulators.**
    - **Confirm which devices you consider are within the scope for this review (reference Attachment A)?**

    The devices within the attachment represent the current market. We would suggest considering the situation of using spinal/epidural hardware for peripheral (ie non-epidural) targets as being in-scope.

2. **The post-listing review will consider available clinical evidence including the 2021 Cochrane Review (*Implanted spinal neuromodulation interventions for chronic pain in adults*).**
    - **Can you provide or point to additional evidence on the comparative clinical effectiveness of spinal cord stimulators compared to standard care, or other therapeutic approaches?**

    ***Studies must be comparative (randomised or appropriately adjusted), include patient-relevant outcomes and have at least medium (4-8 months) and preferably, long term (≥12 months) follow-up.***

    Appendix 1 is an extended critical appraisal of the reference document. In summary, the Cochrane methodology may have resulted in useful studies being excluded from analysis, as well as some seemingly eligible studies having either not been found or ignored. The Cochrane methodology may be poorly suited to drawing conclusions about a number of pain medicine topics. A Cochrane review in 2017 (Eccleston et al) concluded *There is no evidence for the efficacy or safety of methods for reducing prescribed opioid use in chronic pain*, yet the practice has certainly not been abandoned!

3. **Can you provide or point to evidence for the comparative cost-effectiveness of spinal cord stimulators?**

   Cost-effectiveness evidence is scant for most interventions on persistent pain, whether pharmacological, physical, psychological or procedural. Pain Management Programs, for example are accepted as the gold standard of conservative care, but best results in published studies are those which have very rigorous selection of subjects, and are expensive and labour-intensive for a treatment which produces durable but small effect sizes over the long term in a minority of patients, and is not currently considered to be clearly better than shorter, less intensive programs when provided to the general pain population (https://pubmed.ncbi.nlm.nih.gov/30179389/). The approximate total cost of a 3-week intensive PMP is $15-20k. Spinal cord stimulators have large upfront costs and require a mature clinical support infrastructure but can be considered cost-effective if overall health-care utilization is considered. For example, 3 x inpatient ketamine infusions will have a cost of approximately $15-21k per year. If the implant prevents all subsequent ketamine infusions which may have taken place, it will be cost-neutral after 4-5 years.

   So in this context of a field of medical practice where studies are difficult to conduct on a large scale, and where conventional RCT design may in fact not be particularly suitable, (see, for example Bogduk https://doi.org/10.1016/j.inpm.2022.100126 ) cost-effectiveness studies are urgently needed but they must first be preceded by consensus on the best patients to be provided to, as well as the critically important consideration of operator training and skill level. The Clinical Care Standard for Procedures in Pain Medicine - PS11(PM) provides such a framework, in conjunction with the Procedures Endorsement Program of the Faculty.

   A highly relevant point to cost-effectiveness of SNMDs is the level of training and professionalism of those who implant them. FPM has established a credentialling program for specialist pain medicine physicians with a procedural scope of practice but the fact remains that there is no legal barrier to any registered doctor deciding to take up the practice. A significant minority of implanters are not Fellows of FPM, and as such cannot be held to the standard established by FPM. The wide variability of practices and apparent 'leak' of epidural leads into uses outside the epidural space are of ongoing concern to FPM. It is impossible to adequately judge the cost effectiveness of an implant if there is no accountability for indication, level of training or craft group who are implanting the devices.

4. **Can you provide or point to any ongoing trials which may impact the findings of the post-listing review?**

   One example we are aware of is a recent Russell Cole Award winner funded by ANZCA Foundation https://www.anzca.edu.au/profiles/research-grant-outcomes/brain-regions-responsible-for-analgesic-responses This study will potentially provide important insights into the mechanisms which may underlie the analgesic response to SNMDs. Time has not permitted a comprehensive search of trial registries to find other studies.

5. **Can you provide or point to guidelines that are available to guide patient selection and the management of spinal cord stimulation to treat chronic pain?**

   The following links give some guidelines which are relevant.

https://www.neuromodulation.com/ins-guidelines is the collection of guidelines from the peak interest body, but are more concerned with technical aspects of care rather than patient selection.

Recommendations for patient selection in spinal cord stimulation - ScienceDirect represents the current (and ongoing) consensus position within FPM (authored by prominent FPM Fellows)

even though it is now more than a decade old. In the absence of definitive evidence-based guidelines, multidisciplinary decision making and ongoing engagement with a pain management service regardless of outcome represents the standard of care.

The former FPM guidance document on neuromodulation (now retired) as well as the current CCS emphasize the importance of situating this invasive and comparatively risky therapy in the setting of a multidisciplinary assessment process and follow-up, and the undesirability of inadequate follow-up arrangement, especially given the high rate of minor complications and more serious issues such as lead migration and breakage. Best practice management returns the patient to further multidisciplinary care after implantation to ensure full advantage is taken of the gains achieved by the implant. Studies have not looked at whether better medium or long-term outcomes are achieved by this stricture, but it is required by the precautionary principle as well as by common sense that if a patient achieves a pain reduction by any means, they are helped to fully convert it to improved function in accordance with fundamental principles of pain medicine.

FPM has been approached by the Australian Commission for Safety and Quality in Health Care to develop a comprehensive model of care for implantable devices, and while such a model of care would be challenging to develop and implement, it would continue FPM's reputation as a world leader in governance and policy in the area of pain medicine, and is under active consideration by the Board of the Faculty, as it is in alignment with the strategic goals of FPM.

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## Appendix 1: Notes on Cochrane Review

**Selection criteria**

Randomised controlled trials comparing SN MD interventions with placebo (sham) stimulation, no treatment or usual care; or comparing SN MD interventions plus another treatment versus that treatment alone. Participants included over 18-year-olds with noncancer and non-ischaemic pain of longer than three months duration. Primary outcomes were pain intensity and adverse events. Secondary outcomes were disability, analgesic medication use, health-related quality of life and health economic outcomes. Their conclusion was

***15 published studies and 20 ongoing studies were included for analysis. No published studies of dorsal root ganglion stimulation were found and no studies comparing spinal cord stimulation with no treatment or usual care were found.***

Comments:

This represents a fraction of the published output and suggests that care is needed with interpretation of the results. A comprehensive review of neuromodulation in the Lancet some 6 months earlier, including some authors with experience in clinical use of neuro modulation, came to somewhat different conclusions. They reported their findings regarding spinal neuromodulation as *"low-to-moderate quality evidence that SCS is superior to reoperation or conventional medical management for failed back surgery syndrome, and conflicting evidence as to the superiority of traditional SCS over sham stimulation or between different SCS modalities"* The Lancet review included assessments of non-invasive and minimally invasive peripheral and brain stimulation in addition to spinal neuromodulation implants.

Regarding the risks of perceived bias, while industry funding remains essential for the conduct of large-scale prospective studies, bias may exist in the opposite direction. It is often not recognised that SNMD is a treatment of last resort, and as such would not be expected to show outstanding efficacy when being used in patients for whom all other medical treatments have been unsatisfactory. Debate frequently centres around funding of large-scale pragmatic trials by insurers who clearly have a vested interest in saving money, and whose results are as predictably negative as the industry funded trials are positive.

Although O'Connell and colleagues in the Cochrane review report having searched the literature for SNMD intervention trials comparing SCS with no treatment or usual care, they claim to have found no studies. This is again the opposite view to that reported in the Lancet article, which reports on several studies that were analysed comparing different SNMD modalities, For example, *Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain 2017; 158: 669–81.* This would appear to be an eligible trial that was not included in the Cochrane analysis, despite it being quoted as a reference within the review in a paragraph discussing the possible mechanism of benefit for this type of stimulation. The primary end point for this study was not a simple pain intensity rating, but a composite end point defined as a pain intensity reduction by 50% at trial phase, PLUS a pain intensity reduction by 50% at 3 months PLUS no neurological deficit related to the implant. This was a trial using a patient-centred composite end-point which showed a higher rate of response for DRGS than conventional SCS and had a long term follow-up. It was presumably excluded due to the composite end-point but this led to inaccurate conclusions regarding possible efficacy for DRGS when the authors report finding 'no eligible studies to analyze.'

*Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. Neurosurgery 2016; 79: 667–77* represents another study seemingly eligible for analysis by the Cochrane review which reports on long-term follow-up from a randomised controlled trial directly comparing two different modalities of SNMD, and which is not referenced.

*Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 2007; 132: 179–88.* This study represents a published RCT directly comparing SCS versus conventional medical management for neuropathic pain. This again seems to have been overlooked despite being highly relevant (although dated) to the topic of the Cochrane rview.

**Authors' conclusions (Cochrane)**

***We found very low-certainty evidence that SCS may not provide clinically important benefits on pain intensity compared to placebo stimulation. We found low- to very low-certainty evidence that SNMD interventions may provide clinically important benefits for pain intensity when added to conventional medical management or physical therapy. SCS is associated with complications including infection, electrode lead failure/migration and a need for reoperation/re-implantation. The level of certainty regarding the size of those risks is very low. SNMD may lead to serious adverse events, including death. We found no evidence to support or refute the use of DRGS for chronic pain.***

The conclusions reached by the Cochrane reviewers are appropriate given the very limited data on which they had to rely. It is unclear how they did not find any studies at all eligible for inclusion regarding DRGS, Comparisons between neuromodulation modalities and usual care. Such studies clearly exist and have been published in reputable journals and would have been worthy of inclusion to increase confidence in the conclusions of the Cochrane review, which are markedly different from a number of other similar systematic reviews conducted at around the same time or earlier, such as the Lancet review published 6 months earlier or the Mayo Clinic Proceedings review published in 2019 ( Spinal Stimulation for the Treatment of Intractable Spine and Limb Pain *Mayo Clinic Proceedings*, 2019-08-01, Volume 94, Issue 8, Pages 1475-1487)

FPM agrees that adverse outcomes including serious injury and death may occur with SNMD implantation and that there is likely to be under-reporting of these given the lack of systematic follow-up. However, outcomes such as revision rates and minor complications may be misleadingly high given that many chronic pain patients are medically complex and may need explantation to facilitate MRIs for other medical conditions or other treatments. The contribution of poor technique or poor patient selection to high rates of minor complications and revisions is not examined in RCTs but likely represents a significant 'real-world' issue that drives the divergence between the observed rates in RCTs and those in clinical practice.

Points 2,3, and 4 make the assumption that the Cochrane review adequately identified and analysed all available studies, whereas this was clearly not the case. The type of studies requested to be provided (comparative, patient relevant outcomes with long-term follow-up) are well recognised as being a major gap in the literature. This type of evidence is not available for most treatments in chronic pain, including medications and psychological interventions. Given the expense involved, and the level of risk we may well never have evidence of this nature. Consideration of more than the Cochrane review is required in this field.

In the Feb 2023 edition of *Pain,* Prof Elja Kalso editorializes on the limitations of this type of systematic review in pain medicine after a major study of combination pharmacotherapy failed to draw any clinically useful conclusions. Her conclusion is illuminating in the current context.

*The main focus of Cochrane-type systematic reviews and meta-analyses is in the rigorous identification and evaluation of all available evidence using standard methods to minimize errors and bias. Too often the conclusion is that the outcome data were incomplete, and because of the small number of study participants and heterogeneity, no conclusions could be drawn. The reader may feel disheartened after having read an extensive review, which did not provide any answers.*

*The authors are not to be blamed. They did their work meticulously. The problem is in the methods and aims of Cochrane-type systematic reviews that ignore the individual patient and the substance, pain medicine, pharmacology, and psychology. All analyses are processed by the same protocol. The clinician would, however, like to know whether some patients actually benefitted from the combinations of analgesics and the reasons for some patients responding, whereas others do not.*

*Systematic reviews and meta-analyses have brought rigor to the design of clinical trials, but they have not advanced our understanding of the "real substance" in pain research. It is time to reconsider the research methodology that the current evidence is based upon and start asking clinically relevant questions such as why patients may respond differently to the same treatment. Although meticulously performed systematic reviews continue to be valuable, major advances could be made by using individual patient data in analyses and designing large single case studies with enough relevant phenotype data and new outcomes.*

If one examines the most up-to-date Cochrane review for psychological therapies for the management of neuropathic pain in adults, one finds a recommendation against its use based on only 2 RCTs which were eligible for review. The 2013 Cochrane review regarding use of physical conditioning programs as part of a return to work strategy for LBP concluded that there was conflicting or negative impact in the short to medium term and a possible minor effect on long-term sick leave, but such programs have continued to be used widely.

The findings of virtually all systematic reviews of the evidence regarding SNMDs agree that high-quality evidence is needed, not just of efficacy but perhaps more importantly of the characteristics of those likely to respond, whether this is diagnosis-specific, patient-specific or some other indicator of good prognosis. The effect of operator characteristics such as poor operative technique and patient selection on complication rates and efficacy requires urgent examination. Monitoring of safety and efficacy outcomes is outside of the scope of a simple RCT, and considerably more complex.

Future trials are underway which may help settle the issue of efficacy, but certainly the clinical experience of regular referrers and implanters with this therapy is that it can be very valuable in cases of otherwise severe and disabling pain. Parameters for judicious use remain to be established within an evidence-based framework, but the treatment has a scientifically sound rationale and is capable of being studied and used in practice in a way which will allow for safe innovation.

**A/Prof Michael Vagg**

Director of Professional Affairs FPM