MSAC Application 1739

Percutaneous Electrical Nerve Stimulation (PENS) therapy for chronic neuropathic pain

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC).

Table 1 PICO for Percutaneous Electrical Nerve Stimulation (PENS) therapy in patients with chronic neuropathic pain

Component	Description
Population	Patients with chronic peripheral neuropathic pain for at least 3 months that does not *adequately* respond to non-invasive standard treatment such as, physical, psychological and/or pharmacological therapies
Prior test	Local anaesthetic block identification of the peripheral nerve(s) amenable to treatment using PENS, radiofrequency ablation or peripheral nerve stimulation
Intervention	Percutaneous Electrical Nerve Stimulation (PENS) therapy administered by a post specialised pain physician, conducted in an operating room with ultrasound guidance, using 1 or 2 21-gauge needle probes, targeting an identifiable peripheral nerve (s), up to 2 times per year. Other types of PENS that exist in the literature such as electro-acupuncture are not the focus of this application as intended by the applicant.
Comparator/s	Non-invasive standard care Pharmaceutical management such as pregabalin, aspirin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and anti-epileptics. A multidisciplinary suite of complementary therapies that can include non-medicinal therapies such as counselling, exercise, acupuncture, relaxation techniques and psychological treatment. TENS (Transcutaneous Electrical Nerve Stimulation) which uses electrodes placed onto the skin of the patient to apply a gentle electrical current through the skin towards the affected nerve. Implantable peripheral nerve stimulation (MBS Items 39134 & 39138) Subcutaneous implantable peripheral nerve stimulation which involves placement and connection of extension wires to epidural or peripheral nerve electrodes. Peripheral nerve lead or leads, surgical placement of, including intraoperative test stimulation, where the leads are intended to remain in situ long term. Radiofrequency ablation/Pulsed radiofrequency (MBS item 39323) A minimally invasive percutaneous procedure using a catheter probe to apply a high-frequency current to denervate a specific peripheral nerve. May also be considered a relevant comparator for the proposed population.
Outcomes	Safety Serious adverse events Device-related complications Procedure complications Need for treatment cessation/withdrawal Effectiveness Health-Related Quality of Life (HRQoL) - e.g. SF-36 Pain Reduction - measured by VAS, neuropathic pain scale (NPS), numerical rating scale (NRS), or other quantitative measure Proportion of patients undergoing implanted device insertion who could be released from a trial period if PENS has been demonstrated to have sufficient efficacy Healthcare system Reduction in narcotic medication Reduction in use of subcutaneous implantable peripheral nerve stimulation Cost of treatment Cost of adverse events or complications
Assessment questions	What is the safety, effectiveness and cost-effectiveness of Percutaneous Electrical Nerve Stimulation (PENS) therapy versus non-invasive standard care, subcutaneous implantable peripheral nerve stimulation or *radiofrequency ablation/pulsed radiofrequency* in patients with chronic peripheral nerve pain.

HRQoL= Health-Related Quality of Life; NSAIDs= non-steroidal anti-inflammatory drugs PENS=Percutaneous Electrical Nerve Stimulation; TENS=Transcutaneous Electrical Nerve Stimulation

Purpose of application

An application requesting the amendment of Medicare Benefits Schedule (MBS) item 39129 to include Percutaneous Electrical Nerve Stimulation (PENS) therapy for treatment of intractable chronic neuropathic pain was received from MICA MEDICAL PTY LIMITED by the Department of Health.

The clinical claim provided by the applicant is that the use of Percutaneous Electrical Nerve Stimulation (PENS) for the management of chronic peripheral neuropathic pain results in:

- noninferior effectiveness and superior safety compared to subcutaneous implantable peripheral nerve stimulation/surgically placed peripheral nerve leads (where the leads are expected to remain in-situ long-term)
- superior effectiveness and inferior safety compared to conventional pain management (non-interventional).

The MBS item 39138 (surgical placement of peripheral nerve leads for implantable peripheral nerve stimulation) had previously been used to claim PENS therapies, however on 1 March 2022, as recommended by the MBS Taskforce review of pain management MBS items[1], an explanatory note (TN.8.241) was applied to specify that that PENS is not to be claimed under this item. A new MBS item 39129 (percutaneous placement of peripheral nerve leads for implantable peripheral nerve stimulation), to which explanatory note TN.8.241 also applies, was also added to the MBS in 2022, following taskforce review. This application is seeking to modify MBS item 39129 to allow claiming of PENS.

PICO criteria

Population

The proposed population for PENS therapy is:

- Adult patients with chronic peripheral neuropathic pain for at least 3 months that does not *adequately* respond to *non-invasive* standard treatment such as, physical, psychological and/or pharmacological therapies.

The application originally described patients with intractable neuropathic pain. During the PICO process the use of 'intractable' instead of 'chronic' was queried. The applicant clarified that their description of intractable neuropathic pain was intended to imply chronic neuropathic pain and confirmed that the intention is for the proposed population to include patients who have been considered to have chronic neuropathic pain for at least 3 months. It is also noted that describing PENS as a treatment for chronic neuropathic pain may better align with the wording used in the existing MBS item 39129 that the applicant is seeking to amend to include PENS. Additionally, the MBS Review Taskforce has recommended that the term 'intractable' is removed from pain medicine items as it is poorly defined and unclear.

Neuropathic pain

Neuropathic pain can be defined as pain produced by a lesion, abnormality or disease that affects the somatosensory nervous system. Rather than being considered a specific condition to be diagnosed,

[1] Recommendation 16 of the Medicare Benefits Schedule Review Taskforce – Final Report on the Review of Pain Management MBS Items (https://www.health.gov.au/resources/publications/taskforce-final-report-pain-management-mbs-items)

neuropathic pain is considered a clinical description of a particular type of pain (IASP, 2011). Chronic pain is typically defined as pain which has persisted over a period of at least 3 to 6 months (Toth & Moulin, 2013). The diagnosis of chronic neuropathic pain is complex as it possesses a variety of underlying aetiologies. A combination of patient history and clinical assessment is useful in diagnosing a patient with chronic neuropathic pain as it can be detected via other assessments of sensory, motor and autonomic function (Toth & Moulin, 2013). Alternatively, there exists a grading system which describes the plausibility of a patient presenting with neuropathic pain based on their own individual medical history and the pain distribution they report, as well as individual neuroanatomical structure, and (if available) the use of a diagnostic test to confirm the presence of a lesion/disease (Finnerup et al., 2016). Peripheral neuropathic pain is distinct from central neuropathic pain in that it is caused by damage to neurons within the peripheral nervous system rather than the central nervous system.

The symptoms which characterise peripheral neuropathic pain include hypersensitivity and/or inflammation around the site of the damaged nerve. The nociceptive effect has been described as consisting of two distinguishable pains: the first of which is more localised and produces a sharper sensation, whereas the second pain feels more diffuse and induces a duller burning sensation. Chronic peripheral neuropathic pain is characterised when these pain sensations are sustained over a period of at least 3 to 6 months (Toth, 2013). Other symptoms of neuropathic pain include numbness, tingling, and electric shock-like sensations as well as muscle weakness, difficulty moving, or problems with balance (Healthdirect Australia, 2022).

Chronic peripheral neuropathic pain is the focus of the application.

PASC queried the definition of chronic pain and its persistent duration in relation to PENS. PASC accepted the applicant's rationale that pain persisting over a 3-month period was appropriate as it would enable PENS to be provided as an earlier alternative treatment option ahead of other available treatments such as opioids which are not an optimal therapy choice for management of chronic pain and can have adverse safety implications.

At-risk populations

An individual's existing health can impact their risk of developing neuropathic pain. Diabetes mellitus is a known risk factor for peripheral neuropathic pain, with almost 50% of cases of diabetes developing diabetic sensorimotor polyneuropathy (DSP) within 10 years of onset. Among patients with DSP, approximately 50% (about 25% of all people with diabetes) will experience neuropathic pain (The Diabetes Control and Complications Trial Research Group, 1993). Other health conditions including stroke, cancer, or multiple sclerosis can also increase the risk of developing neuropathic pain, while pathogenic causes of neuropathy have also been identified, these include viruses such as SARS-CoV-2, HIV, Zika, varicella zoster, and Hepatitis (A, B, C, and E) as well as bacteria and toxins including leprosy, Lyme, tetanus, diphtheria, and botulism (Tran et al., 2022).

Prevalence

In Australia, it has been estimated that chronic neuropathic pain affects 5.2% of the population, with greater risk of chronic neuropathic pain being observed among persons who are female, aged over 45 years, or reside in areas with lower scores on the socio-economic index (Henderson et al., 2016).

Utilisation estimates

The application suggested that in Australia there are between 1000 and 2000 needle probes sold each year. If PENS is being used 1 to 3 times each year per patient as suggested by the application, there are approximately between 333 and 2000 patients in Australia who would use PENS annually. In 2022, MBS item 39129 was claimed 69 times and item 39138 was claimed 1,391 times. Previously, in 2021, item 39138 was claimed 2,669 times. This shows a difference in claims of 1,209 following the restriction on item 39138 and addition of item 39129. This suggests that between 403 and 1,209 patients may utilise PENS therapies each year (assuming between 1 and 3 treatments per year per patient).

Current management

At present, treatment for neuropathic pain in Australia consists of both medicinal and non-medicinal treatments which can be non-invasive or invasive. Medications used to treat neuropathic pain include painkillers such as aspirin, paracetamol, or non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and anti-epileptic drugs may also be effective in relieving neuralgia (Healthdirect Australia, 2022). Pregabalin is indicated for use as a neuropathic pain relief for Australian adults and uptake as a common treatment for neuropathic pain has significantly increased in the population over the last decade (Cheng et al., 2023). In an analysis by Finnerup et al. (2018), pregabalin was identified as the medication which appeared most in published studies examining the effectiveness of drugs at treating neuropathic pain. Meta-analyses by Finnerup et al. (2018) and Cheng et al. (2023) of pregabalin and other drugs used to treat neuropathic pain suggested that the therapeutic efficacy of these drugs in relieving pain had reduced across different studies over time, reflecting improvements in study design quality, to include larger sample sizes, longer follow-up durations and more robust outcome measurement over this period of time.

Non-medicinal non-invasive treatments for neuropathic pain include counselling, exercise, acupuncture, relaxation techniques, psychological treatment, and transcutaneous electrical nerve stimulation (TENS) (Healthdirect Australia, 2022). An individual who is experiencing chronic neuropathic pain may be treated using a combination of these therapies and can be referred to a multidisciplinary pain clinic by their doctor to produce a personalised pain management plan. As pain management, and indeed, the experience of pain itself can be unique to different people there is not necessarily a single prescribed form of standard care for neuropathic pain but rather treatment should be tailored to the needs of each individual.

In addition, there are a suite of invasive treatments available that are added as an adjunct to the above non-invasive methods that aim to remediate long-term neuropathic conditions including radiofrequency ablation, pulsed radiofrequency, or subcutaneous implantable peripheral nerve stimulation which all target peripheral nerves.

Patients unsuitable for PENS

Children, patients with a localised infection or an irreversible increased bleeding tendency are not recommended for PENS treatment.

The applicant's pre-PASC response did not confirm the suitability of PENS for patients who are pregnant or have epilepsy but did indicate that heart disease does not contraindicate the use of PENS in general but that PENS should not be used across the patient's chest.

The application refers in several places to the use of PENS for treatment of pain restricted to a highly localised region of allodynia which would occur earlier in treatment algorithms. During the PICO process the applicant confirmed that this application is specific for patients with chronic peripheral neuropathic

pain and that they can experience allodynia as an associated symptom. However, patients who are experiencing allodynia without chronic neuropathic pain are not considered the focus of this application. An extension of the indication to include patients experiencing allodynia without chronic neuropathic pain would likely require a separate or substantially reworked application with accompanying evidence.

Intervention

PENS is a therapeutic technology consisting of an electrical pulse generator that is connected to one or two 21-gauge needle probes which are inserted percutaneously into the tissue directly in contact with or adjacent to the pain producing nerve. Activated PENS provides the nerve with electrical current. A single session of active PENS treatment is recommended to last for 25 minutes, to align with the optimal duration of PENS for relieving pain estimated by Hamza et al. (1999). PENS treatment is recommended to be repeated at most 2-3 times each year. A patient's response to PENS may also be able to provide information to inform future treatment selection such as whether the use of an implanted peripheral nerve simulation device is likely to be effective. PENS treatment can be delivered as a day procedure. It requires use of an operating theatre and ultrasound to detect the specific nerve which is causing pain and guide the needle probe(s) to the appropriate area. During treatment, the patient is to be given light sedation. PENS is to be administered by a physician who has attained a post-specialisation in pain medicine.

PASC queried whether the procedure was required to be performed in an operating theatre with anaesthesia and ultrasound as stated by the applicant given the photographic evidence of the procedure being performed in a consultation room. PASC also queried whether the use of anaesthetic during the PENS procedure may contribute to the patient's subjective perception of pain relief following the treatment. The applicant clarified that saline solution or skin local anaesthetic can be used during the procedure and patients with severe allodynia may require the use of anaesthetics to tolerate the insertion of the electrode through the skin. The applicant also clarified that the use of an operating theatre was not always necessary unless patients were to undergo general anaesthesia or sedation (in the case of patients with severe allodynia). The use of general anaesthesia in patients experiencing pre-existing allodynia, versus using local anaesthesia for electrode insertion in patients without allodynia can be explored in the assessment phase. PASC considered it reasonable to restrict the frequency of PENS to 2 per year.

It is claimed in the application that the mechanism of action underlying PENS is the same as other peripheral nerve stimulation technologies including electro-acupuncture. PENS provides a sensation of paraesthesia or muscle contraction and the potentially analgesic effect experienced by PENS patients has been hypothesised to act on inhibitory interneurons around the spinal cord to impede the pain sensation (de Sire et al., 2021). This is thought to stimulate serotonin, cholinergic, and opioid receptors within the spinal cord, producing an analgesic effect.

PENS will likely be used as an adjunct to existing non-invasive treatments for chronic pain which include medicinal, psychological and physical therapies. PENS is expected to displace some use of implanted nerve stimulating devices to a later line of treatment and may replace the use of these devices altogether amongst some patients.

According to Vajramani (2020), PENS encompasses four different neurostimulator technologies that are available to treat neuropathic pain. Typically distinguished by their brand/manufacturer names. Other distinguishing features of these technologies include the area targeted (superficial vs named peripheral nerve) and the size or number of the needles used. The 4 treatments have different schedules with some

used multiple times per week and others only used a couple of times per year. The four technologies include:

1. electro-acupuncture PENS targeting peripheral nerves (approximately 10 needle probes)
2. PENS delivered by an array of small needles to target superficial nerves
3. PENS delivered by a flexible electrode that is inserted via a needle to target a peripheral nerve
4. the PENS treatment described by the applicant as 1-2 21-gauge needle probes targeting a named peripheral nerve or unnamed peripheral nerve endings.

An initial scan of available effectiveness evidence for PENS identified five studies of which only two (Raphael et al. (2011) and Rossi et al. (2016)) appear to relate to the type of PENS intended by the applicant (#4 above). The other 3 studies (Hamza et al., 1999, 2000; Weiner et al., 2008) involve the use of 10 needle probes consistent with #1 above.

PASC queried the potential application of other forms of PENS to be used within the described population and noted the applicant's advice that the PENS intervention specific to this application is distinguished using one to two 21-gauge needle probes.

The Neuromodulation Society of Australia and New Zealand website states that there are around 150 neuromodulators available between the two countries. According to the applicant, physicians who are likely to administer PENS require a pain medicine post-specialisation and are also likely to be fellows of the aforementioned Society. This suggests that there will be a relatively fixed number of qualified physicians who can provide this treatment.

For the evaluation stage, the accessibility and availability of PENS may need to be taken into account in contrast with comparative therapies.

Comparator(s)

The comparators described in the application include (i) standard treatment and (ii) subcutaneous implantable peripheral nerve stimulation

<u>Non-invasive standard care</u>

Standard treatment of chronic neuropathic pain typically consists of a multidisciplinary suite of complementary therapies and can include non-medicinal therapies such as counselling, exercise, acupuncture, relaxation techniques and psychological treatment. In addition to these, patients will likely also use pharmaceuticals to manage their pain. Pregabalin, aspirin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and anti-epileptics have been indicated for use among patients with chronic neuropathic pain.

Transcutaneous Electrical Nerve Stimulation (TENS), a therapy which applies a gentle current to a nerve via electrodes placed onto the skin would precede PENS in the line of treatment as it is less invasive and may also provide a viable treatment option for patients. Therefore, TENS would also fall under the classification of standard care in comparison with PENS.

For the evaluation stage, there may be a need to define what is included under the umbrella of 'standard care' to ensure that the evidence base used is making practical comparisons between PENS and alternative treatments as would occur in clinical care.

PENS may be conceptualised as an adjunct to standard non-invasive care which is likely to have ongoing utilisation, whereas PENS would be likely to replace the use of the other comparators described below.

Neuromodulation therapy - implantable peripheral nerve stimulation

Subcutaneous implantable peripheral nerve stimulation provides analgesic effects for the relief of chronic neuropathic pain using the same mechanism of action as PENS. These devices can be more practical than PENS for certain patients as they offer more regular nerve stimulation, and because the device is embedded under the skin long-term, the financial cost to the patient may be less than the cost of PENS treatment provided on an as-needed basis. The applicant described subcutaneous implantable peripheral nerve stimulation as utilising a combination of two MBS items, item 39134 (which includes the neurostimulator) and item 39138 (which consists of surgically placed peripheral nerve leads) which are listed below. PENS is intended to come prior to longer term surgically implanted devices in the treatment algorithm and in some cases may replace them. Subcutaneous implantable peripheral nerve stimulation is also a comparator to PENS. These implants use the same mechanism of action to stimulate nerves as PENS.

In the clinical management algorithm proposed by Bates et al. (2019), neuromodulation therapies such as implantable peripheral nerve stimulation are considered part of the fourth line of treatment for neuropathic pain, and should be considered after neuropathic pain has persisted for 6 months or longer.

The MBS item numbers below (Table 2 and Table 3) are currently utilised for subcutaneous implantable peripheral nerve stimulation treatments.

Table 2 The MBS listing for item 39134

Item Number	Category	Group	Subgroup	Subheading
39134	3 – Therapeutic Procedures	T8 – Surgical Operations	7 - Neurosurgical	2 – Pain Relief
Description				
Neurostimulator or receiver, subcutaneous placement of, including placement and connection of extension wires to epidural or peripheral nerve electrodes, for the management of chronic neuropathic pain or pain from refractory angina pectoris (H) Multiple operation rule (Anaes.) (Assist.) Fee: $360.05 Benefit: 75% = $270.05				

Source: mbsonline.gov.au – accessed 12 May 2023

Table 3 The MBS listing for item 39138

Item Number	Category	Group	Subgroup	Subheading
39138	3 – Therapeutic Procedures	T8 – Surgical Operations	7 - Neurosurgical	2 – Pain Relief
Description				
Peripheral nerve lead or leads, surgical placement of, including intraoperative lead stimulation, for the management of chronic neuropathic pain, where the leads are intended to remain in situ long term (H) Multiple operation rule (Anaes.) (Assist.) Fee: $712.65 Benefit: 75% = $534.50				

Source: mbsonline.gov.au – accessed 12 May 2023

Interventional therapy - pulsed radiofrequency/ablation (PRF)

PRF uses a high-frequency current to lesion a specific nerve, this inhibits the nociceptive sensation transmitted from the nerve, providing the patient with a reprieve from the feeling of pain. The applicant indicated that PRF may be used up to three times each year on a single nerve and the treatment can be claimed under MBS item number 39323 (Table 4) which describes the percutaneous denervation of peripheral nerves, however, the item recommends the use of thermal radiofrequency in most cases rather than pulsed radiofrequency and states that radiofrequency therapies can be used on any given nerve up to six times in a 12-month period. The Bates et al. (2019) clinical algorithm (see Clinical Management algorithm section below) considers this to be part of the third line of treatment, preceding neuromodulation treatments including implanting nerve stimulating devices which fall under the fourth line of treatment.

Pulsed radiofrequency treatments are minimally invasive but require penetration of the skin to target peripheral nerves with either a needle probe (in the case of PENS) or a catheter (in radiofrequency). According to Chang (2018), there is a lack of evidence which supports the use of pulsed radiofrequency on relieving peripheral neuropathic pain.

The applicant's pre-PASC response did not formally propose a clinical claim for PENS versus PRF in and has indicated that it is their view that PRF may be a precursor to PENS, however, this is not reflected in their proposed clinical management algorithm which displays PENS as preceding PRF.

PASC acknowledged that PRF has a different mechanism of action to PENS and the applicant comments that PRF may be less effective than PENS. However, PASC noted that PRF is an alternative treatment to PENS in the clinical algorithm. After discussing with the applicant, PASC confirmed that for the purposes of a health technology assessment, PRF is an appropriate comparator to PENS. However, the applicant claimed that PENS would have superior effectiveness compared to PRF and that PRF would not be able to inform on future use of peripheral nerve stimulator implants. PASC advised that evidence to support the applicant's claim that PENS has superior effectiveness compared to PRF should be evaluated during the assessment phase.

Table 4 The MBS listing for item 39323

Item Number	Category	Group	Subgroup	Subheading
39323	3 – Therapeutic Procedures	T8 – Surgical Operations	7 - Neurosurgical	3 – Peripheral Nerves
Description				
Percutaneous denervation (excluding medial branch nerve) by cryotherapy or radiofrequency probe, other than a service to which another item applies, applicable not more than 6 times for a given nerve in a 12 month period Multiple operation rule (Anaes.) Fee: $292.60 Benefit: 75% = $219.45 85% = $248.75				

Source: mbsonline.gov.au – accessed 12 May 2023

Outcomes

Safety

- Serious adverse events
- Device-related complications

- Procedure complications
- Need for treatment cessation/withdrawal

No specific safety outcomes were specified in the application, but the above suggested safety outcomes would be appropriate to include.

Effectiveness

- Pain reduction – Measured by VAS, neuropathic pain scale (NPS), numerical rating scale (NRS), or other quantitative measure.
- Health Related Quality of Life (HRQoL) - Measured by questionnaire (e.g. SF-36, EQ-5D)

For the evaluation stage, a defined list of appropriate measures to quantify pain relief will be required so that the evidence base used will comprise reliable and valid measures of pain which can provide insight into the clinical effectiveness of PENS.

Healthcare system

- Reduction in use of narcotic medication
- Reduction in use of subcutaneous implantable peripheral nerve stimulation
- Costs of treatment
- Cost of adverse events or complications

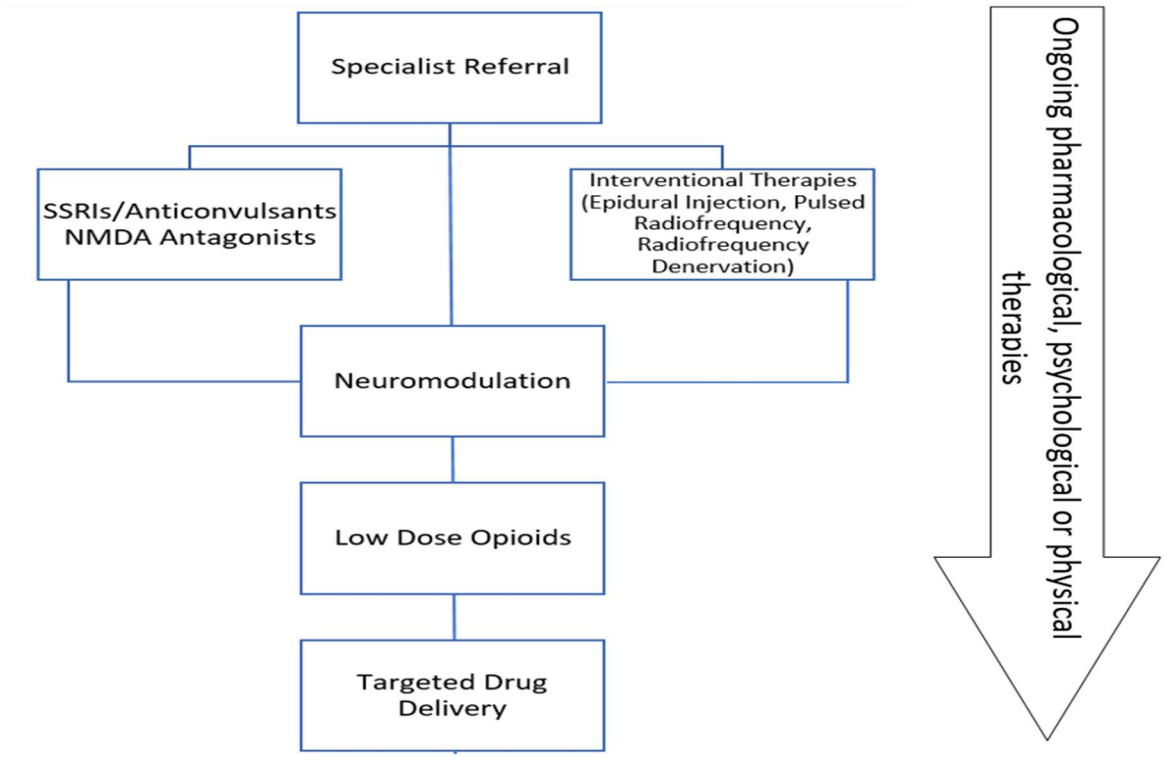
Although not mentioned in the application, other outcomes relevant to the health care system are likely to include cost of treatment, cost of adverse events or complications and financial implications.

PASC agreed that the outcomes listed above were appropriate to be used in the assessment phase.

Clinical management algorithms

The clinical management algorithm for the management of neuropathic pain has been described by Bates et al. (2019) and is summarised in Figure 1. It includes the comparative treatments relevant to this application. As the population eligible for PENS has been described as patients with chronic pain (lasting >3 months) that does not adequately respond to non-invasive standard treatment such as, physical, psychological and/or pharmacological therapies, it can be assumed that individuals treated in this algorithm have completed either a 4–6-week trial of a first line pharmaceutical treatment (tricyclic antidepressants, SNRIs, gabapentinoids, or topical treatments) and/or a 6-8 week trial of first line multidisciplinary care and another 4–6-week trial of second line treatment (tramadol or combination therapy), yielding an inadequate response from both lines of treatment, before reaching the beginning of this algorithm.

Figure 1 The Bates et al (2019) clinical management algorithm for chronic neuropathic pain



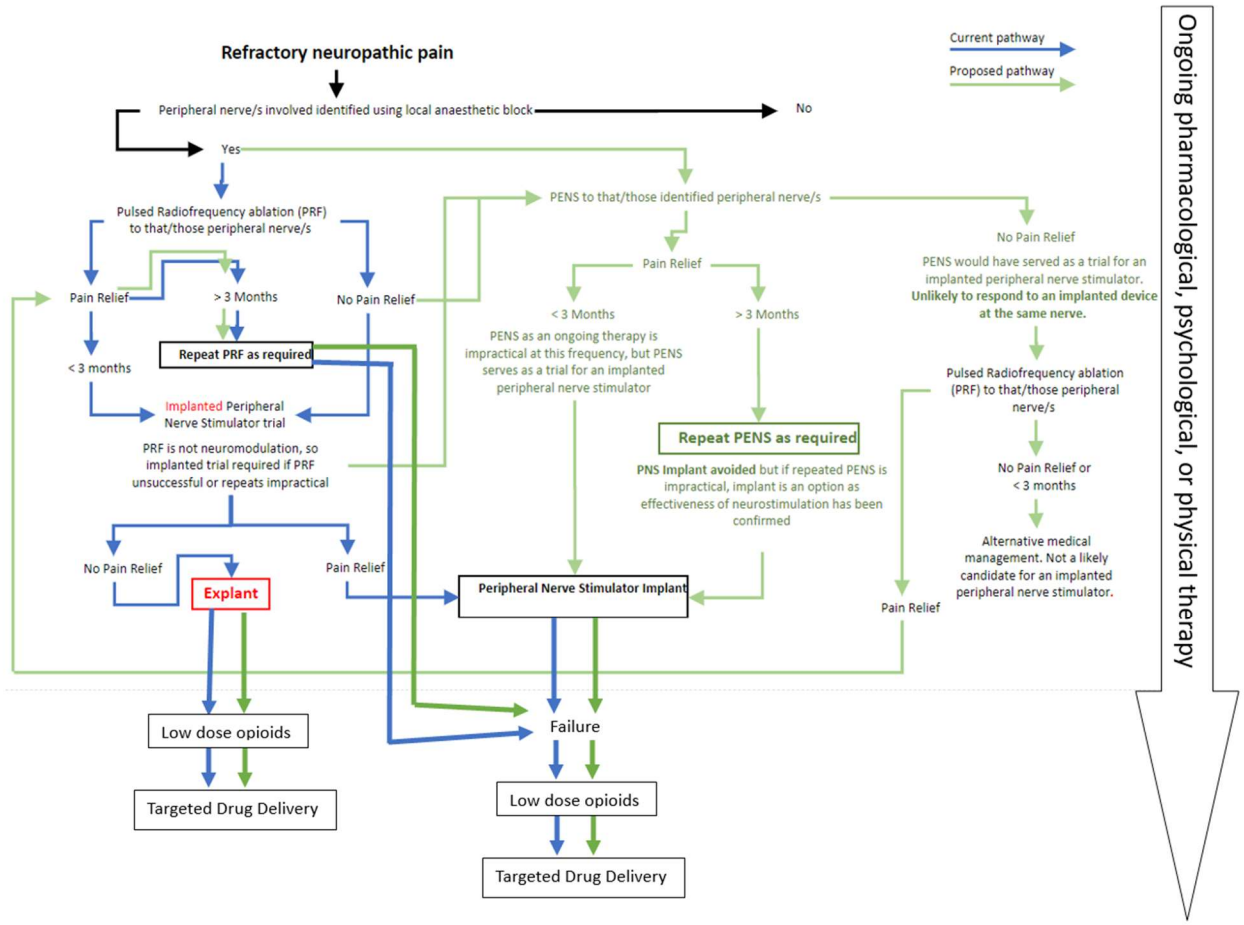
NMDA= N-Methyl-D-aspartic acid; SSRIs=Selective serotonin reuptake inhibitors

Source: Adapted from Figure 1 from Bates et al (2019)

Pulsed radiofrequency occurs following specialist referral but before neuromodulation treatments including implanting nerve stimulating devices. Neuromodulation is to be considered if pain has persisted for over 6 months and is distressing/disabling (measured with Brief Pain Inventory Inference scores or QoL measures). Neuromodulation should be trialled for between 1 and 4 weeks and will go ahead permanently if the patient experiences pain relief of >50% and are satisfied with the treatment. Alongside these treatments is the use of ongoing pharmacological, psychological, or physical therapies. Any one of these stages could be the endpoint of the algorithm if they are able to provide sufficient pain relief to the patient.

Figure 2 is the clinical algorithm provided by the applicant and amended during the PICO process and begins with patients having reached a point at which their neuropathic pain is considered refractory, and the noxious nerve can be identified. Looking only at the green PENS pathway above, PENS is provided before pulsed radiofrequency treatment, which is only included in the algorithm if PENS has no effect. If the effect of PENS lasts for over 3 months, then PENS is used repeatedly to treat the pain. If the effect of PENS does not last for more than 3 months, then patients will be treated with subcutaneous implantable peripheral nerve stimulation. Additional pathways following the failure of PRF and IPNS have been included as well as showing the ongoing utilisation of non-invasive standard care to assist with pain management throughout all treatment courses. These additional pathways have been taken from the Bates et al (2019) algorithm in Figure 1.

Figure 2 Amended applicant proposed clinical management algorithm



PENS=Percutaneous Electrical Nerve Stimulation; PRF= Pulsed Radiofrequency ablation

Source: Page 13 of MSAC 1739 Application PICO Set, amended during the PASC process to include standard non-invasive management and treatment with low dose opioids and pharmacology following failure of PRF and IPNS.

The applicant justified their use of this clinical management algorithm around the premise that subcutaneous implantable peripheral nerve stimulation represents the main comparator to PENS and the algorithm they have provided displays the proposed advantages PENS holds over this other technology, including its less invasive application and its potential use to inform future treatment choices. The application claims that PENS can assess the suitability of a patient for subcutaneous implantable peripheral nerve simulation as both PENS and the implantable devices use the same form of electrical stimulation. The application claims that if a patient does not respond to PENS, they would be unlikely to respond to subcutaneous implantable peripheral nerve stimulation. Hence PENS may be used to help inform future treatment selection.

For the evaluation stage, a clinically significant level of pain relief will need to be defined to allow comparisons to be made between different evidence sources and to provide a point of reference against which the clinical claim of effectiveness can be assessed.

There are some notable differences between the applicant proposed clinical algorithm (Figure) and the Bates et al (2019) clinical management algorithm (Figure 1). The algorithm by Bates et al. (2019), states that neuromodulation should only begin if pain has persisted for 6 months after patients were initially diagnosed with neuropathic pain. In contrast, Figure 2 would commence after the patient has had pain that persisted for a minimum of 3 months.

Figure 2, as proposed by the applicant, places pulsed radiofrequency after neuromodulation, whereas radiofrequency therapies precede neuromodulation in the Bates et al (2019) algorithm. This leads to a divergence of opinion regarding where PENS should sit in the treatment algorithm with two options described:

1. Based on the first algorithm adapted from Bates et al. (2019) PENS would commence at the beginning of the neuromodulation stage of treatment before consideration of more invasive neuromodulation (subcutaneous implantable peripheral nerve stimulation). An implication may be that radiofrequency therapies would have been trialled in the previous line of treatment and would not be a direct comparator with PENS.
2. Alternatively, the applicant's algorithm suggests that PENS should be considered following specialist referral, serving as a direct comparator with radiofrequency therapies as well as implantable peripheral nerve stimulation.

Standard non-invasive pain care continues across both algorithms so the use of PENS would be an adjunct and an alternative under both options above.

The Bates et al. (2019) algorithm is not as comprehensive as that suggested by the applicant in outlining alternative lines of treatment that may either precede or follow neuromodulation.

PASC discussed the amended version of the proposed clinical algorithm including PENS. PASC noted the current treatment path is for patients to undergo PRF and that the proposed inclusion of PENS would provide patients an alternative treatment option to PRF. Further that if PENS is unsuccessful, patients could then try PRF or vice versa. As noted earlier, PASC concluded that PRF is an appropriate comparator to PENS.

PASC queried the applicant's claim that PENS can be used instead of trialling an implantable peripheral nerve stimulating device. A clinical expert representing the applicant confirmed that PENS is used as a screening tool for referring patients to surgeons who implant the implantable peripheral nerve stimulating device and that the availability of PENS reduces the number of referrals. Evidence that PENS can be used in exchange for the trial procedure for an implantable peripheral nerve stimulating device altogether will need to be presented and evaluated during the assessment phase.

Proposed economic evaluation

There are likely to be two relevant comparators- standard non-invasive care and subcutaneous implantable peripheral nerve stimulation, with a possible third comparator of pulsed radiofrequency/ablation. The clinical claims are summarised by comparator in Table 5 along with recommended economic evaluation method.

Table 5 Summary of clinical claims for PENS by comparator and recommended economic evaluation method.

Comparator	Clinical effectiveness claim	Safety claim	Recommended economic evaluation
Standard non-invasive care	PENS superior	PENS inferior	CUA
Subcutaneous implantable peripheral nerve stimulation	PENS non-inferior	PENS superior	CEA/CUA
Radiofrequency ablation / pulsed radiofrequency	PENS superior	Uncertain	CEA/CUA

CEA=cost-effectiveness analysis; CUA= cost utility analysis; PENS= percutaneous electrical nerve stimulation

As all these chronic neuropathic pain interventions are intended to improve quality of life, the MSAC guidelines suggest that a cost-utility analysis (CUA), rather than a cost-effectiveness analysis (CEA), would be the preferred method of economic evaluation.

Table 6 provides a guide for determining which type of economic evaluation is appropriate.

Table 6 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety		Comparative effectiveness		
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence
Cells shaded yellow correspond with non-invasive standard care
Cells shaded red correspond with implantable nerve stimulating devices and radiofrequency ablation/pulsed radiofrequency

PASC queried whether there is any direct comparative effectiveness of PRF with PENS. Without direct comparative evidence, it would mean a naïve indirect comparison would be required to assess the applicant's claim that PRF may be less effective compared to PENS, including the ability to inform whether a patient would be a suitable candidate for an implantable peripheral nerve stimulator device.

The applicant did not provide further comments but indicated that the cost of anaesthetic is included in their estimation of the cost of PENS to the patient.

Table 7 provides a brief overview of some of the initial effectiveness evidence identified as available to inform economic evaluation. The applicant identified five effectiveness studies which are summarised. Only two studies by Rossi et al. (2016) and Raphael et al. (2011) involve the use of PENS as described by the applicant (a single needle probe). The other three studies involve use of electro-acupuncture PENS which is not the focus of this application. The study by Raphael et al. (2011) was unable to complete its crossover and only measured pain immediately before and after PENS treatment but not after any extended period. Rossi et al. (2016) is therefore the most relevant of these studies to assess PENS as it would be administered in clinical practice. Rossi et al. (2016) included 76 patients who received PENS for chronic neuropathic pain and were followed-up after 6 months, however, this trial did not involve a control group. Supplementary observational evidence and indirect comparisons may be required to populate an economic evaluation for the three comparators described above.

Table 7 Key Characteristics of studies which assessed the effectiveness of PENS as a pain relief therapy

	Author Name (year)	Sample Size	Population	PENS Treatment	Control	Alternative treatments also permitted?	Results	Notes
Studies relevant to the specific type of PENS that is the subject of this application								
1	Rossi (2016)	76	Participants aged 18 to 80 years old with peripheral neuropathic pain lasting >3 months	Single needle probe used for one-off 25 minute dose of PENS	None	Yes	Median (IQR) Neuropathic Pain Scale decreased from 6.4 (4.6-8.2) to 2.1 (0.8-4.1) after six months and Median (IQR) Numerical Rating Scale decreased from 8 (7-10) to 3 (0-6) after six months	7 participants received a second dose of PENS during follow-up
2	Raphael (2011)	31	Patients aged 23 to 84 years old who had experienced pain for >6 months and had a localised area of hyperalgesia	Single needle probe used for one-off 25 minute dose of PENS	Sham PENS	Patients who had previously experienced pain relief from previous treatments were excluded	Median (range) Numerical Rating Scale decreased from 7.5 (6-10) to 0.5 (0-8.5) and Mean (range) pain pressure threshold increased from 202gm (55-800) to 626gm (45-800)	Comparison made pre and post treatment, no specified follow-up. Crossover did not occur due to loss of blinding after second treatment
Studies relevant to other types of PENS that are not the subject of this application								
3	Weiner (2008)	200	Participants aged ≥65 years old who had daily back pains lasting for over 3 months	10 needle probes used for one 30 minute dose of PENS given twice a week for 6 months	Stimulation at T12 dermatome just above lumbar region and/or general conditioning and exercise	Yes	All groups reported reductions in McGill Pain Questionnaire scores	Control PENS probably was effective in relieving pain as it was applied to adjacent dermatomes
4	Hamza (2000)	50	Adults with Type II diabetes who had painful peripheral neuropathic pain for >6 months in their legs/feet	10 needle probes used for one 30 minute dose of PENS given three times a week over three consecutive weeks	Sham PENS	Yes	In the active group mean (SD) VAS pain scores reduced from 6.2 (±1) to 2.5 (±0.9) and mean (SD) analgesic consumption reduced from 3.3 (±1.3) pills/day to 1.3 (±0.6) pills/day. The control group saw no significant difference in pain score or analgesic consumption	

	Author Name (year)	Sample Size	Population	PENS Treatment	Control	Alternative treatments also permitted?	Results	Notes
5	Hamza (1999)	75	Participants aged 21-76 who had lower back pain that had persisted for >3 months	10 needle probes used for varying durations 3 times per week for 2 consecutive weeks	None	Yes	PENS had the most pain relieving effect after a 30 minute dose, then a 45 minute dose, then a 15 minute dose, and lastly a 0 minute dose. Analgesic use also decreased significantly for participants who received 30 minute or 45 minute doses of PENS	

IQR= interquartile range; PENS=percutaneous electrical nerve stimulation; SD= standard deviation; VAS= Visual Analogue Scale

PASC expressed concern with the quantity and quality of evidence for the use of PENS in the published literature cited by the applicant. PASC noted that only two of the five cited studies were relevant to the specific type of PENS that is the subject of this application. PASC highlighted a number of issues with the two studies including the small sample sizes used as well as the fallibility of sham PENS treatments when used as a comparator. PASC queried whether, in light of the evidence limitations, the population should be further refined.

Proposal for public funding

The applicant has not proposed any amendments MBS item 39129 itself, rather the applicant has proposed amending the associated explanatory note TN.8.241 to remove the statement specifically excluding the use of PENS in order to allow PENS to be claimed under MBS item 39129. The MBS item 39129 and the applicant's proposed amendments to the explanatory note TN8.241 for MBS item 39129 are below (with changes shown using blue strikethrough text).

For the evaluation stage, it should be noted that TN.8.241 pertains to both item 39129 and item 39138. If this note is amended, there needs to be consideration if PENS can be claimed under item 39138.

Table 8 Applicant proposed amendment to MBS item 39129 and associated explanatory note TN.8.124

Category (3) – THERAPEUTIC PROCEDURES
MBS item 39129 Peripheral lead or leads, percutaneous placement of, including intraoperative test stimulation, for the management of chronic neuropathic pain (H) Multiple Operation Rule (Anaes.) (Assist.) (See para TN.8.241 of explanatory notes to this Category)
Fee: $641.40 Benefit 75% = $481.05
Explanatory note TN.8.241 Placement of peripheral nerve leads for the management of chronic intractable neuropathic pain (Items 39129 and 39138) Items 39129 and 39138 are for the insertion of leads that are intended to remain in situ long term. ~~Percutaneous Electrical Nerve Stimulation (PENS) is not to be claimed under these items.~~ ~~The use of PENS for the management of chronic pain has not been assessed by the Medical Services Advisory Committee (MSAC) or recommended for public funding. Therefore, PENS procedures for management of chronic pain cannot be billed under the MBS, including items 39129 and 39138.~~ Item 39138 is the appropriate item to claim when surgical lead placement is required for a trial procedure prior to longer term placement. Item 39129 is the appropriate item for the percutaneous placement of leads, including for trial procedures. Items 39129 and 39138 provide for the insertion of one or multiple leads. There is no intention to change current billing practices for these items, e.g. where more than one lead may be billed as part of an episode.

For the evaluation stage, there needs to be consideration if the MBS item description needs to be amended to specifically exclude some other forms of PENS (e.g. electroacupuncture PENS) or whether there is a need for a separate MBS item for this treatment rather than removal of the note.

The application stated that the proposed change to MBS item 39129 could lead to a reduction in use of MBS items 39138 and 39134 which are currently used for implantable therapies. The justifications provided by the applicant include:

- Successful treatment with PENS may relieve pain sufficiently meaning that an implantable (or other ongoing standard treatment) is no longer needed
- The responsiveness of a patient to PENS may provide information that indicates a patient is unsuitable for further treatment with an implantable therapy
- Patients may prefer PENS for being less invasive

During the PICO process it was clarified by the applicant that MBS item 39129 is only used by post specialised pain medical practitioners. The use of PENS would involve use of an operating theatre, guided ultrasound and light sedation.

PASC noted that ultrasound may be used when inserting the PENS probes but confirmed that MBS items for ultrasound should not be co-claimed with PENS, consistent with previous advice regarding co-claiming ultrasound guidance.

The proposed fee is the same as that already associated with this item number. The applicant noted that it is anticipated that patients will incur out-of-pocket costs of approximately $1000 (due to gap payments to

pain proceduralist and anaesthetist), however the true cost of the fee-for-service is at the discretion of the medical pain practitioners involved.

PASC considered it reasonable to restrict the frequency of PENS to 2 per year.

PASC discussed the proposed cost of PENS, querying the higher cost of the PENS electrode needles compared with similar needle technologies. Further, PASC raised the issue of equity regarding the accessibility of PENS given that chronic neuropathic pain is more prevalent among lower socio-economic status (SES) populations. That is, PASC was concerned about the high out-of-pocket fee of approximately $1000 which could have implications for equitable patient access with a disproportionate effect on patients of lower SES. The applicant suggested that the potential out-of-pocket costs for PENS is similar to other treatments and that the costs of PENS is similar to PRF. A breakdown (and justification) of the proposed MBS fee and total costs associated with PENS is required for the assessment phase.

Summary of public consultation input

Consultation Feedback

PASC noted and welcomed consultation feedback from five organisations and one individual who works as an anaesthetist. The five organisations that submitted input were:

- Australian Society of Anaesthetists (ASA)
- Medtronic Australasia (Medtronic)
- Neuromodulation Society of Australia and New Zealand (NSANZ)
- Private Healthcare Australia (PHA)
- The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG).

The consultation feedback received was largely supportive of public funding for percutaneous electrical nerve stimulation (PENS) therapy for chronic neuropathic pain. The consultation feedback raised some concerns in relation to the limited clinical data, in particular as a screen for implanted neuromodulation devices.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included reduction in pharmacotherapy use in patients, particularly opioids, greater choice and access to treatment options and the ability. Other benefits included increased functioning for patients allowing return to work and social activities, and a less invasive alternative method of neurostimulation for patients unsuitable for implantable devices.

The main disadvantages of public funding received in the consultation feedback included limited clinical and outcomes data, treatment likely not curative, variable duration of benefit, and the potential for PENS to be used in addition to implantable neuromodulation trials. Other disadvantages included managing patient expectations as treatment not guaranteed to succeed and patients may not adhere to the proposed treatment regimens as some require multiple sessions.

Psychological assessment for suitability was identified as another service required prior to delivery of the intervention.

Indication(s) for the proposed medical service and clinical claim

All of the consultation feedback agreed with the proposed population. Most of the feedback received agreed with the clinical claims and the comparator being implanted PNS, with only Medtronic disagreeing with the clinical claims and that implanted PNS is a suitable comparator.

Additional comments

Medtronic raised concerns that PENS could potentially delay progression to implantable PNS and that there is little evidence that PENS could be used as a surrogate trial for implantable PNS. The ASA members reported that PENS therapy was useful to treat neuropathic pain in appropriately selected patients prior to the removal of PENS from MBS item number 39138. The ASA note that there is support for PENS therapy by international bodies such as the NHS. PHA recommend that the further details in the service descriptor states 'PENS (or directly comparable technology) therapy probes'. They added that claims that PENS can identify patients who would not benefit from neurostimulation using and implanted neuromodulator should be thoroughly assessed in the health technology analysis.

PASC noted the consultation feedback was mostly supportive of PENS. PASC noted the dissenting views on whether PENS can be used in place of trialling an implantable peripheral nerve stimulation device. However, PASC noted that, if there is evidence to substantiate that PENS can be used in exchange for the trial procedure for an implantable peripheral nerve stimulation device then, the feedback highlighted that the costs with trialling the implantable peripheral nerve stimulation device could be avoided.

Next steps

PASC noted that at the time of the meeting the applicant was undecided on whether or not they would be developing the assessment report and have subsequently advised they have elected to progress the application as an ADAR (Applicant Developed Assessment Report).

Applicant comment on the ratified PICO Confirmation

The applicant did not confirm that allodynia was not the focus of the application. Allodynia is NOT a separate population and does not require an extension to the indication. Allodynia and hypersensitivity are different ways of describing the same symptom which is a characterising symptom of neuropathic pain. Allodynia (hypersensitivity) is not a separate condition but a component of peripheral neuropathic pain and as such, is included within the definition of peripheral neuropathic pain.

> The symptoms which characterise peripheral neuropathic pain include hypersensitivity and/or inflammation around the site of the damaged nerve. The nociceptive effect has been described as consisting of two distinguishable pains: the first of which is more localised and produces a sharper sensation, whereas the second pain feels more diffuse and induces a duller burning sensation. Chronic peripheral neuropathic pain is characterised when these pain sensations are sustained over a period of at least 3 to 6 months (Toth, 2013). Other symptoms of neuropathic pain include numbness, tingling, and electric shock-like sensations as well as muscle weakness, difficulty moving, or problems with balance (Healthdirect Australia, 2022).

In terms of PENS Probe placement, it may be placed at a named peripheral nerve, or at the unnamed nerve endings in an area of allodynia if there is no named nerve to target.

According to Vajramani (2020), PENS encompasses four different neurostimulator technologies. It should also be noted that examples (1) [electro-acupuncture PENS targeting peripheral nerves (approximately 10

needle probes)] and (2) [PENS delivered by an array of small needles to target superficial nerves] include needles which are not long enough to reach named peripheral nerves.

A PRF Probe/Needle has an active/electrically conductive tip of between 2mm and 10mm, whereas a PENS Probe has an active/electrically conductive length of between 20mm and 200mm. If PRF was to be used to stimulate the same target, several PRF Probes/Needles would need to be used where one PENS probe is sufficient in length. PRF was not designed for the same purpose.

The applicant's clinical algorithm was an attempt to document the complexity of chronic neuropathic pain management. At first look, it may appear that the PRF and PENS are direct comparators, however this is not the case. Both therapies are included in both arms, where if one therapy is ineffective, the other therapy is trialled, but in different sequence. Success with one therapy effectively rules out effectiveness of the other therapy as the mechanism of action is different.

Both clinical experts who attended the PASC meeting considered that a comparative study of PENS vs PRF would be unethical.

Additionally, PRF has no role in determining whether an implantable neurostimulator is likely to be successful, as the mechanism of action is not the same as neurostimulation.

Should PRF be unsuccessful when used as a first line therapy, then the subsequent alternative therapies (comparators) are PENS or an implantable neurostimulator.

References

Bates, D., Schultheis, B. C., Hanes, M. C., Jolly, S. M., Chakravarthy, K. V., Deer, T. R., Levy, R. M., & Hunter, C. W. (2019). A Comprehensive Algorithm for Management of Neuropathic Pain. *Pain Medicine*, *20*(Supplement_1), S2–S12. https://doi.org/10.1093/pm/pnz075

Chang, M. C. (2018). Efficacy of Pulsed Radiofrequency Stimulation in Patients with Peripheral Neuropathic Pain: A Narrative Review. *Pain Physician*, *21*(3), E225–E234.

Cheng, E. T. L., Cheik-Hussein, M., Lin, N., Lewin, A. M., McAuley, J. H., & Harris, I. A. (2023). A meta-epidemiological study on the reported treatment effect of pregabalin in neuropathic pain trials over time. *PLoS ONE*, *17*(1), 1–17. https://doi.org/10.1371/journal.pone.0280593

de Sire, A., Ammendolia, A., Lippi, L., Farì, G., Cisari, C., & Invernizzi, M. (2021). Percutaneous Electrical Nerve Stimulation (PENS) as a Rehabilitation Approach for Reducing Mixed Chronic Pain in Patients with Musculoskeletal Disorders. *Applied Sciences*, *11*(9), 4257. https://doi.org/10.3390/app11094257

Finnerup, N. B., Haroutounian, S., Baron, R., Dworkin, R. H., Gilron, I., Haanpaa, M., Jensen, T. S., Kamerman, P. R., McNicol, E., Moore, A., Raja, S. N., Andersen, N. T., Sena, E. S., Smith, B. H., Rice, A. S. C., & Attal, N. (2018). Neuropathic pain clinical trials: Factors associated with decreases in estimated drug efficacy. *PAIN*, *159*(11), 2339. https://doi.org/10.1097/j.pain.0000000000001340

Finnerup, N. B., Haroutounian, S., Kamerman, P., Baron, R., Bennett, D. L. H., Bouhassira, D., Cruccu, G., Freeman, R., Hansson, P., Nurmikko, T., Raja, S. N., Rice, A. S. C., Serra, J., Smith, B. H., Treede, R.-D., & Jensen, T. S. (2016). Neuropathic pain: An updated grading system for research and clinical practice. *Pain*, *157*(8), 1599–1606. https://doi.org/10.1097/j.pain.0000000000000492

Hamza, M. A., Ghoname, E. A., White, P. F., Craig, W. F., Ahmed, H. E., Gajraj, N. M., Vakharia, A. S., & Noe, C. E. (1999). Effect of the duration of electrical stimulation on the analgesic response in patients with low back pain. *Anesthesiology*, *91*(6), 1622–1627. https://doi.org/10.1097/00000542-199912000-00012

Hamza, M. A., White, P. F., Craig, W. F., Ghoname, E. S., Ahmed, H. E., Proctor, T. J., Noe, C. E., Vakharia, A. S., & Gajraj, N. (2000). Percutaneous electrical nerve stimulation: A novel analgesic therapy for diabetic neuropathic pain. *Diabetes Care*, *23*(3), 365–370. https://doi.org/10.2337/diacare.23.3.365

Healthdirect Australia. (2022, December 7). *Neuropathy* [Text/html]. Healthdirect Australia. https://www.healthdirect.gov.au/neuropathy

Henderson, J., Pollack, A. J., Pan, Y., & Miller, G. C. (2016). Neuropathic and non-neuropathic chronic pain at GP encounters: Prevalence, patient characteristics, suffering and pregabalin use. *Australian Family Physician*, *45*(11), 783–786.

IASP. (2011). *Terminology | International Association for the Study of Pain*. International Association for the Study of Pain (IASP). https://www.iasp-pain.org/resources/terminology/

Metro Pain Group (n.d.). *Fact Sheet Percutaneous Electrical Nerve Stimulation (PENS)* [html]. Metro Pain Group. https://www.metropain.com.au/wp-content/uploads/2020/03/Fact-sheet_PENS_2017_09.pdf

Raphael, J. H., Raheem, T. A., Southall, J. L., Bennett, A., Ashford, R. L., & Williams, S. (2011). Randomized Double-Blind Sham-Controlled Crossover Study of Short-Term Effect of Percutaneous Electrical Nerve Stimulation in Neuropathic Pain. *Pain Medicine*, *12*(10), 1515–1522. https://doi.org/10.1111/j.1526-4637.2011.01215.x

Rossi, M., DeCarolis, G., Liberatoscioli, G., Iemma, D., Nosella, P., & Nardi, L. F. (2016). A Novel Mini-invasive Approach to the Treatment of Neuropathic Pain: The PENS Study. *Pain Physician*, *19*(1), E121-128.

The Diabetes Control and Complications Trial Research Group. (1993). The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *New England Journal of Medicine*, *329*(14), 977–986. https://doi.org/10.1056/NEJM199309303291401

Toth, C. (2013). Peripheral and central sensitization. In C. Toth & D. E. Moulin (Eds.), *Neuropathic Pain: Causes, Management and Understanding* (pp. 51–64). Cambridge University Press. https://doi.org/10.1017/CBO9781139152211.006

Toth, C., & Moulin, D. E. (Eds.). (2013). The Clinical Presentation of Neuropathic Pain. In *Neuropathic Pain: Causes, Management and Understanding* (pp. 1–32). Cambridge University Press. https://doi.org/10.1017/CBO9781139152211.002

Tran, H., Smith, D. I., & Chen, E. (2022). Infectious Neuropathies. In D. I. Smith & H. Tran (Eds.), *Pathogenesis of Neuropathic Pain: Diagnosis and Treatment* (pp. 249–280). Springer International Publishing. https://doi.org/10.1007/978-3-030-91455-4_13

Vajramani, G. (2020). Percutaneous Electrical Nerve Stimulation for Facial Pain. In K. V. Slavin (Ed.), *Progress in Neurological Surgery* (Vol. 35, pp. 45–59). S. Karger AG. https://doi.org/10.1159/000509621

Weiner, D. K., Perera, S., Rudy, T. E., Glick, R. M., Shenoy, S., & Delitto, A. (2008). Efficacy of Percutaneous Electrical Nerve Stimulation and Therapeutic Exercise for Older Adults with Chronic Low Back Pain: A Randomized Controlled Trial. *Pain*, *140*(2), 344–357. https://doi.org/10.1016/j.pain.2008.09.005