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Neuromodulation for Cancer and Non- Cancer Pain

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Abbreviations

AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
BC	British Columbia
BPI	Brief Pain Inventory
BPS	British Pain Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence Interval
CLI	Critical Limb Ischemia
CNS	Canadian Neuromodulation Society
CMM	Conventional Medical Management
CRPS	Complex Regional Pain Syndrome
CSF	Cerebrospinal Fluid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EAN	European Academy of Neurology
EFIC	The European Pain Federation
EFNS	The European Federation of the Neurological Societies
FBSS	Failed Back Surgery Syndrome
FIQ	Fédération Interprofessionnelle de la santé du Quebec
HF10	High Frequency 10 kHz
HIQA	Health Information and Quality Authority
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
HTR	Health Technology Reassessment
ICD-11	International Classification of Diseases 11 th Revision
ICER	Incremental Cost Effectiveness Ratio
ICSI	Institute for Clinical Systems Improvement
INS	International Neuromodulation Society
IPG	Interventional Procedure Guidance
MAiD	Medical Assistance in Dying

NAAC	National Assessment and Accreditation Council
NICE	National Institute for Health Care Excellence
NPRS	Numeric Pain Rating Scale
NTAC	National Technical Assistance Center
ONS	Occipital Nerve Stimulation
OR	Operating Room
PCN	Primary Care Network
PCS	Pain Catastrophizing Scale
PENS	Percutaneous Electrical Nerve Stimulation
PNS	Peripheral Nerve Stimulation
PNfS	Peripheral Nerve Field Stimulation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RQIA	Regulation and Quality Improvement Authority
SCS	Spinal Cord Stimulation
SPG	Sphenopalatine Ganglion
TENS	Transcutaneous Electrical Nerve Stimulation
tSNS	Transcutaneous Supraorbital Nerve Stimulation
UBC	University of British Columbia
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
VGH	Vancouver General Hospital

1 Executive Summary

This report presents the findings and conclusions of a provincial health technology assessment on neuromodulation for chronic pain; that is: spinal cord stimulation for cancer and non-cancer pain, transcutaneous supraorbital nerve stimulation for non-cancer pain, peripheral nerve stimulation and peripheral nerve field stimulation for non-cancer pain, and intrathecal pumps for cancer and non-cancer pain. The primary research questions were:

1. What is the clinical effectiveness of these neuromodulation technologies? What is the clinical effectiveness in comparison to alternatives such as opioids?
2. What are patients' perspectives and experiences with these neuromodulation technologies?
3. How are these neuromodulation technologies used in British Columbia (BC)? How does this use compare to clinical guidelines and practices in other jurisdictions?
4. What are the cost effectiveness and potential budget impact of using these neuromodulation technologies in comparison to other available alternatives?
5. What gaps exist in the literature, and what areas of future work have been identified, if any?

Background: Chronic pain has far-reaching impacts on an individual's personal and professional life, and on society in general. Multiple treatments exist for chronic pain depending on the physiology and etiology of the condition. Following failure or intolerance of more conservative treatments neuromodulation may be an option for a sub-group of patients. Neuromodulation involves targeted delivery of a chemical, biological, or electrical stimulus in order to modulate nervous system activity. Technologies of interest for this report include spinal cord stimulation (SCS), intrathecal pumps, peripheral nerve stimulation (PNS), peripheral nerve field stimulation (PNfS), and transcutaneous electrical nerve stimulation (TENS) of the supraorbital nerve.

Methods: The following methodological approaches were used to gather and synthesize the available evidence:

- I. Systematic review and grey literature review of health technology assessments on neuromodulation
- II. Systematic Review on clinical effectiveness of neuromodulation

- III. Review of guidelines and best practice recommendations
- IV. Systematic review of patient perspective literature
- V. Patient Interviews
- VI. Contextual analysis to understand the current utilization of neuromodulation in British Columbia
- VII. Environmental scan across Canada
- VIII. Cost effectiveness and budget impact analysis
- IX. Summary of emerging applications and technologies

Key findings:

Evidence on effectiveness of the different types of neuromodulation were mixed, resulting in a range of recommendations for the different neuromodulation types. Fifteen RCTs were identified assessing SCS in non-cancer pain with nine presenting significant reductions in pain measures. No RCTs were identified assessing SCS in cancer pain. Four RCTs were identified assessing intrathecal pumps in cancer pain, three of which reported significant reductions in pain measures and 4 RCTs assessed intrathecal pumps in non-cancer pain, only one of which reported significant reductions in pain measures. Six RCTs were identified assessing PNS in non-cancer pain with four presenting significant reductions in pain measures and 1 RCT assessed PNfS in non-cancer pain; it reported significant reductions in pain measures. Finally, 1 open-label study assessed supraorbital TENS and reported inconclusive efficacy and safety results.

A Canadian jurisdictional scan was completed. Responses were received from Calgary, Edmonton, Saskatoon, London, Toronto, Montreal, Quebec City, and Halifax. Of these locations, SCS and PNS are currently offered for non-cancer pain at all locations. PNfS, TENS and intrathecal pumps are less common being offered by less than half of the respondents. SCS is used substantially more (over 200 cases annually) than other neuromodulation treatments (approximately 100 cases annually combined) for non-cancer pain.

There are currently four BC hospital-affiliated pain programs providing some neuromodulation for pain: one in Vancouver Coastal (St. Paul's Hospital), two on Vancouver Island (Royal Jubilee Hospital in Victoria, Nanaimo Regional Hospital), and one in the North (Prince George

Hospital). St. Paul's hospital is the referral site for the most complex patients. In the past year approximately 40-45 neuromodulation devices were implanted in new patients, the majority of these being SCS (35 to 40 implanted). There are an estimated 400 patients living with neuromodular implants currently being supported in BC (Vancouver Coastal - ~260; VIHA - ~90; Northern - ~55).

Based on clinician interviews, the clinical experience is that neuromodulation is highly effective for specific sub-groups of patients. Clinicians within the BC programs report a 80-90% success rate, defined primarily as improved function, improved quality of life, and decreased pain. It was noted repeatedly that neuromodulation is only successful when embedded in a multi-disciplinary pain clinic/program.

Five studies were identified reporting the patient experience with neuromodulation.

The primary themes emerging across four of the five studies were: the individuality and complexity of the experience of living and coping with chronic pain; the challenges of deciding upon and obtaining a neuromodulation device; adapting to and using neuromodulation as a strategy for better managing pain; and, the positive impacts of neuromodulation with respect to both pain reduction and improving function and quality of life. A key theme emerging from the fifth study, was the importance of the patient-surgeon relationship as an influencing factor in a patient's comfort level with having their structural spine surgeon also perform the surgery to implant SCS device. Interviews with patients and families in BC echoed these findings. Patients stressed the way people were treated at the pain clinic, including being listened to, believed, and treated with dignity, respect, and compassion. They also noted that neuromodulation needs to be embedded in a good pain program; it can't stand alone. In addition, for these patients, neuromodulation has made a substantial positive difference to their quality of life; with most saying they are not sure they would still be here without it.

Four implementation options were developed based on the evidence herein. These options include: discontinuing public funding for neuromodulation; maintaining the status quo; developing St. Paul's as the only center for neuromodulation; and developing a more coordinated approach to neuromodulation across the five regional health authorities. With an assumed

annual incidence of SCS device insertion of 0.02/1,000 people, approximately 89.0 SCS devices will be inserted across British Columbia each year. In the scenario in which pain clinics without fluoroscopy suites are developed in the Northern Health region and Interior Health region to support neuromodulation, but all device insertions occur at St. Paul's Complex Pain Program, expected costs over five years are \$44.7 million. In a strategy that develops pain clinics in the Northern Health region and Interior Health region where simple device insertions occur in-region and St. Paul's Complex Pain Program handles only the complex device insertions, expected costs over five years are \$46.1 million.

Conclusions:

High quality evidence supporting SCS use in specific chronic non-cancer pain conditions and intrathecal pump use in chronic cancer pain was found. All other conditions and neuromodulatory techniques require further research to determine clinical effectiveness and safety. Key patient and clinician informants indicated neuromodulation was very effective and impactful in the right circumstance. Four implementation options were developed, each option has implementation and feasibility considerations as well as additional budgetary requirements.

2 Purpose of this Health Technology Assessment

The purpose of this health technology assessment (HTA) was to synthesize the evidence to inform the development of policy for the use of neuromodulation for patients with cancer and non-cancer pain. This report summarized evidence of the current literature of clinical effectiveness, current practice and usage in British Columbia, clinical experience, patient experience, cost-effectiveness and budget impact analysis.

3 Research Question and Research Objectives

The primary research questions are:

1. What is the clinical effectiveness of neuromodulation, specifically:
 - a. spinal cord stimulation for cancer and non-cancer pain,
 - b. transcutaneous supraorbital nerve stimulation for non-cancer pain
 - c. peripheral nerve stimulation for non-cancer pain,
 - d. peripheral nerve field stimulation for non-cancer pain,
 - e. intrathecal pumps for cancer and non-cancer pain?
2. What are patients' perspectives and experiences with the above types of neuromodulation?
3. How are the above types of neuromodulation used in BC? How does this use compare to clinical guidelines and practices in other jurisdictions?
4. What are the cost effectiveness and potential budget impact of the above types of neuromodulation in comparison to other available alternatives?
5. What gaps exist in the literature, and what areas of future work have been identified, if any?

4 Overview of Approach

A variety of methodological approaches were used to gather and synthesize the available evidence in order to address the primary research question (Figure 1). The following methodologies were used:

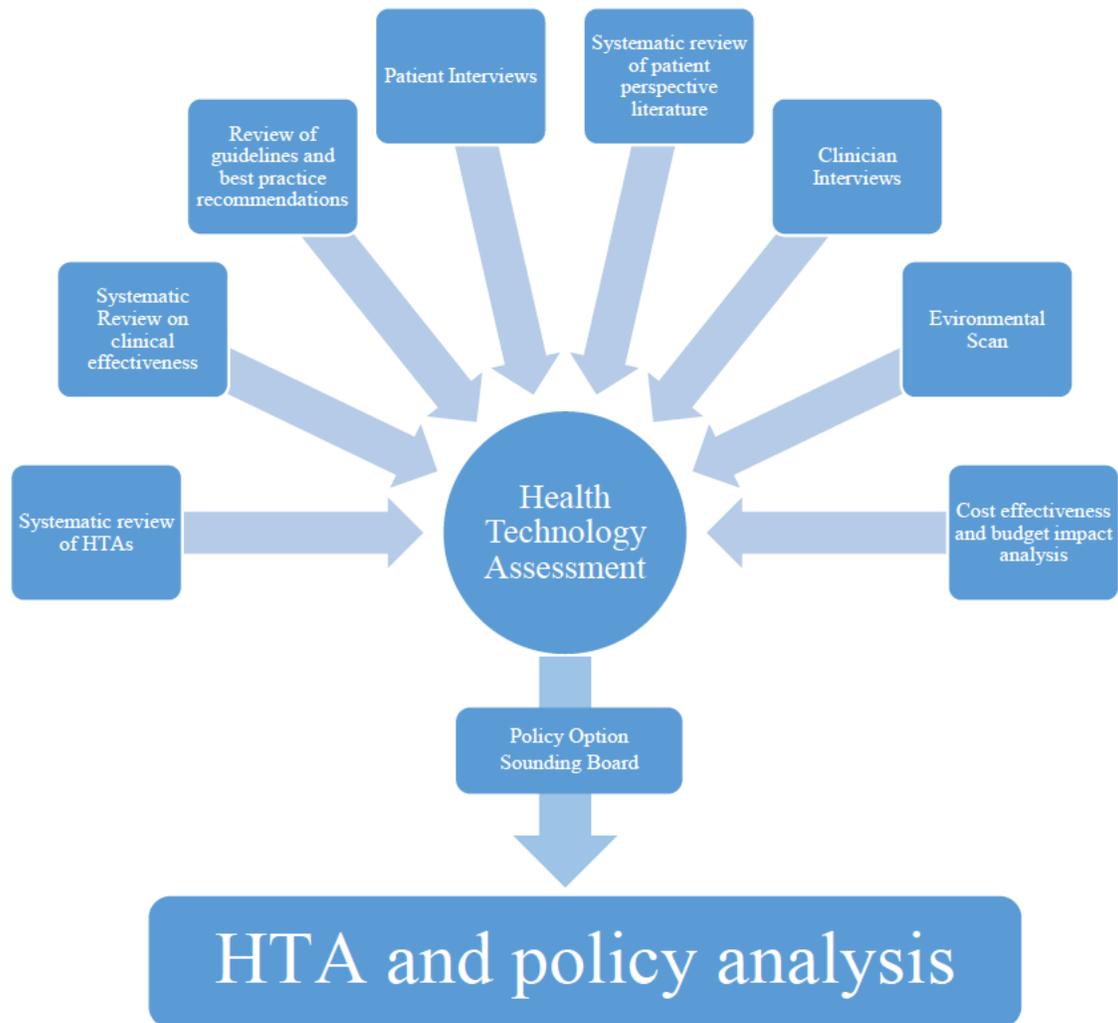
- I. Systematic review and grey literature review of health technology assessments on neuromodulation
- II. Systematic Review on clinical effectiveness of neuromodulation
- III. Review of guidelines and best practice recommendations
- IV. Systematic review of patient perspective literature
- V. Patient Interviews
- VI. Contextual analysis to understand the current utilization of neuromodulation in British Columbia
- VII. Environmental scan across Canada
- VIII. Cost effectiveness and budget impact analysis
- IX. Policy analysis

The neuromodulation technologies and patient populations within scope of this health technology reassessment are presented in Table 1.

Table 1. Neuromodulation technologies and patient populations in scope of this health technology assessment

Technology	Population	
	Cancer	Non-Cancer
Spinal cord stimulation	✓	✓
Transcutaneous supraorbital nerve stimulation	---	✓
Peripheral nerve stimulation	---	✓
Peripheral nerve field stimulation	---	✓
Intrathecal pump	✓	✓

Figure 1. Summary of Process



5 Background

5.1 Chronic Pain

Pain is defined as a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components¹. Pain lasting beyond an expected period of healing or for more than 3-6 months is generally categorized as chronic.^{2,3} Pain can be classified as nociceptive, neuropathic, or a mixture of the two. Nociceptive chronic pain results from damage and inflammation of tissue that stimulates pain receptors called nociceptors. Nociceptive pain can be superficial, activation of superficial skin and tissue nociceptors, or deep, activation

of somatic (e.g. muscles, tendons, bones) or visceral (organs) nociceptors.⁴ Neuropathic chronic pain can be attributed to damage or disease of the somatosensory nervous system. Neuropathic pain originates in the central nervous system (brain and spinal cord), or the peripheral nervous system.⁵ Refractory or persistent chronic pain is difficult to treat and management is an ongoing healthcare challenge. It can be debilitating and greatly reduce quality of life impacting not only the physical, but also the social and emotional facets of one's life. The estimated economic burden of chronic pain in Canada is 50-60 billion dollars per year as of 2011. ^{6 as cited in 7}

5.1.1 Classification of chronic pain

There are seven suggested categories of chronic pain for the 11th edition of the International Classification of Diseases (ICD-11), chronic primary pain, chronic cancer pain, chronic posttraumatic pain, chronic neuropathic pain, chronic headache and orofacial pain, chronic visceral pain, and chronic musculoskeletal pain (Box 1).⁸ The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) includes one chronic pain disorder, somatic symptom disorder.⁹

5.1.2 Cancer versus Non-cancer Pain

Cancer pain is conceptualized as any pain resulting from cancer. This can include pain due to tumor progression, tumor invasion, related surgeries, systemic treatments, related infections, inactivity, and fatigue. Non-cancer pain constitutes all other pain. The chronic nature of the pain is determined based on the same time criteria for both categories of pain. The partition of cancer pain as an isolated category of pain is a recent development; the use of the term "cancer pain" has increased in frequency over the past three decades.¹⁰ The term non-cancer pain began being employed approximately two decades after the concept of cancer pain was introduced. The distinction between cancer and non-cancer chronic pain has recently been called into question due to the physiology of the pain not being linked to its etiology.^{11,12} The development of the separate categories was driven largely by different philosophies of treatment for the two patient groups. Differences in social/contextual and psychological components of patient groups were hypothesized to warrant different treatment trajectories and thus different pain categories as well.¹³ Opioids were promoted for treatment of cancer over non-cancer pain despite similar evidence bases for opioid treatment in either patient group. Despite lack of robust scientific and

clinical evidence for the conceptual separation of the pain categories, the terms cancer and non-cancer pain are heavily employed in the literature.

Box 1. Chronic Pain Classification for the ICD-11

Chronic pain (persistent or recurrent pain lasting longer than 3 months)

1. Chronic primary pain
 - 1.1. Widespread chronic primary pain (including fibromyalgia syndrome)
 - 1.2. Localized chronic primary pain (including nonspecific back pain, chronic pelvic pain)
 - 1.x. Other chronic primary pain
 - 1.z. Chronic primary pain not otherwise specified
2. Chronic cancer pain
 - 2.1. Chronic pain due to cancer and metastases
 - 2.2. Chronic chemotherapy-induced pain (primary parent: chronic neuropathic pain)
 - 2.3. Chronic pain due to cancer surgery (primary parent: chronic postsurgical and posttraumatic pain)
 - 2.4. Chronic pain due to radiotherapy
 - 2.x. Other chronic pain related to cancer
 - 2.z. Chronic cancer pain not otherwise specified
3. Chronic postsurgical and posttraumatic pain
 - 3.1. Chronic postsurgical pain
 - 3.2. Chronic posttraumatic pain
 - 3.x. Other chronic postsurgical and posttraumatic pain
 - 3.z. Chronic postsurgical and posttraumatic pain not otherwise specified
4. Chronic neuropathic pain
 - 4.1. Peripheral neuropathic pain
 - 4.2. Central neuropathic pain
 - 4.x. Other neuropathic pain
 - 4.z. Neuropathic pain not otherwise specified
5. Chronic headache and orofacial pain
 - 5.1. Chronic primary headaches
 - 5.2. Chronic secondary headaches
 - 5.3. Chronic orofacial pains†
 - 5.z. Headache and orofacial pain not otherwise specified
6. Chronic visceral pain
 - 6.1. Chronic visceral pain from persistent inflammation
 - 6.2. Chronic visceral pain from vascular mechanisms
 - 6.3. Chronic visceral pain from obstruction/distension
 - 6.4. Chronic visceral pain from traction/compression
 - 6.5. Chronic visceral pain from combined mechanisms
 - 6.6. Chronic visceral pain referred from other locations
 - 6.7. Chronic visceral pain from cancer (primary parent: chronic cancer pain)
 - 6.8. Functional or unexplained chronic visceral pain (primary parent: chronic primary pain)
 - 6.x. Other chronic visceral pain

- 6.z. Chronic visceral pain not otherwise specified
- 7. Chronic musculoskeletal pain
 - 7.1. Chronic musculoskeletal pain from persistent inflammation
 - 7.2. Chronic musculoskeletal pain from structural osteoarticular changes
 - 7.3. Chronic musculoskeletal pain due to disease of the nervous system (All neuropathic pain will be classified under 4. Chronic neuropathic pain. Here, other chronic musculoskeletal pain originating from diseases of the nervous system, eg, spastic pain will be listed.)
 - 7.4. Chronic nonspecific musculoskeletal pain (primary parent: chronic primary pain)
 - 7.x. Other chronic musculoskeletal pain syndromes
 - 7.z. Chronic musculoskeletal pain not otherwise specified

5.1.3 Prevalence of Chronic Pain

Chronic pain has a multitude of etiologies. From ageing effects, to injury and disease, chronic pain can be a complex condition without obvious underlying cause. Leading causes of chronic pain include past injuries and surgeries, back issues, migraines and headaches, arthritis, nerve damage, infections, and fibromyalgia.¹⁴ A 2007/8 Canadian Community Health Survey estimated approximately 1 in 10 Canadians experience chronic pain.¹⁵ Higher prevalence of chronic pain was reported with increased age, lower level of educational attainment, and among the indigenous population.¹⁵ A Canadian Pain Association funded survey was conducted in 2011 and estimated the prevalence of chronic pain in individuals over 18 at 18.9%.¹⁶ Approximately half of those reporting chronic pain had been suffering for more than ten years.

5.1.4 Impact of chronic pain

Chronic pain is recognized to produce significant economic and social burden, affecting not only the patient, but also their social circles and their larger society.¹⁷ The impacts of chronic pain are far-reaching and varied, negatively impacting ability to perform daily personal and professional activities, physical and mental health, and family and social relationships.^{18,19} Severity of pain can vary resulting in a range of impacts, from limitations on intensity of physical activity to inability to perform essential activities.²⁰ The same range of impact can be seen in social, psychological, and professional contexts. Economically, costs are derived both directly through healthcare use and indirectly through loss of productivity.^{21,22} In comparison with other chronic diseases, pain is associated with the worst quality of life.²³

5.1.5 Diagnosis

Since pain is a subjective phenomenon there are few specific tests for diagnosis of chronic pain. The duration of the pain and the etiology are clinically assessed in order to determine diagnosis and subsequent treatment. Various physical examinations and blood and imaging diagnostics can help confirm diagnosis. Neuropathic pain can be diagnosed based on medical history, review of systems, physical and neurological examination, appropriate laboratory studies, magnetic resonance imaging, and electrophysiological studies.²⁴ Questionnaires and assessment of pain quality and presence of lesions of the nervous system can also be employed to aid the diagnostic process.²⁵

5.1.6 Treatment

Multiple clinical guidelines for specific chronic pain conditions exist and are summarized in the clinical guideline review section (Section 8). Pain management strategies can range from topical and oral medications to nerve blocks and surgical procedures. Certain anticonvulsants can be used in the treatment of neuropathic pain²⁶. Analgesic medications can range from nonsteroidal anti-inflammatory drugs to opioids. More invasive pain management procedures can range from implantation of an intrathecal pump to peripheral nerve and spinal cord stimulation. Various therapies such as cognitive behavioral and exercise therapy can also be used in treatment of chronic pain. Patient demographics and personal circumstances along with the etiology and severity of the pain play a role in determining the best treatment plan.

5.1.7 Neuromodulation

When conventional pain therapies fail or cause intolerable side effects, neuromodulation may be a treatment option. Neuromodulation involves targeted delivery of a chemical, biological, or electrical stimulus in order to modulate nervous system activity.²⁷ Common means of clinical neuromodulation include electrical or magnetic stimulation (neurostimulation) and intrathecal drug administration. Electrical neurostimulation can be achieved through implantation of electrodes at a targeted site of intervention or through less invasive transcranial and transdermal applications. Intrathecal drug administration is achieved through implantation of a pump, typically sub-dermally in the abdomen, and an attached catheter connected to the intrathecal

space of the spine. Both interventions allow for more direct stimulation electrically and chemically than that provided through oral and topical therapies.

5.1.8 Neurostimulation

Analgesic effects of electrical stimulation date back to 5th dynastic Egyptian tomb reliefs of electric Nile catfish²⁸ and medical reports in 47CE describing accidental contact with torpedo fish curing pains of gout,²⁹ predating our knowledge of electricity itself. With the development of new technologies, our understanding and breadth of interventions greatly expanded. Modern neurostimulatory techniques have recently gained popularity in western medical practice for a variety of conditions. Neurostimulation has a wide range of applications beyond pain management.^{30,31} Transcranial and deep brain stimulation are employed in movement and affective disorders and a variety of devices, such as pacemakers and cochlear implants, aid in treatment of cardiac disorders and sensory deficits. Within the context of chronic pain management, a number of neurostimulatory interventions exist with varying levels of supporting evidence. SCS, TENS of the supraorbital nerve, PNS, and PNfS will be the neurostimulatory interventions focused on in this report. An overview of the neurostimulation technology and clinical conditions within this report are outlined in Table 2.

Table 2. Summary of Neurostimulators

Neurostimulators	Description	Clinical Conditions
Spinal Cord Stimulation	Small implantable device that electrically stimulates the spinal cord. There are three main types: traditional, burst, and high frequency stimulation.	<ul style="list-style-type: none"> • Failed Back Surgery Syndrome • Complex Regional Pain Syndrome • Chronic Inoperable Limb Ischemia • Diabetic Neuropathy • Refractory Angina • Pain Resulting from Cancer
Transcutaneous Electrical Stimulation of the Supraorbital Nerve	Self-adhesive electrodes stimulate supraorbital nerve through the skin.	<ul style="list-style-type: none"> • Chronic Headache/Migraine • Supraorbital Neuralgia
Peripheral Nerve Stimulation	Small device and electrodes implanted percutaneously or directly at site of peripheral nerve of interest for electrical stimulation.	<ul style="list-style-type: none"> • Complex Regional Pain Syndrome • Variety of Neuralgias • Variety of Peripheral Neuropathies • Nerve Injuries
Peripheral Nerve Field	Small device and electrodes	<ul style="list-style-type: none"> • Complex Regional Pain

Stimulation	implanted in the subcutaneous tissue in the area of focalized pain for electrical stimulation.	Syndrome <ul style="list-style-type: none"> • Variety of Neuralgias • Variety of Peripheral Neuropathies • Nerve Injuries
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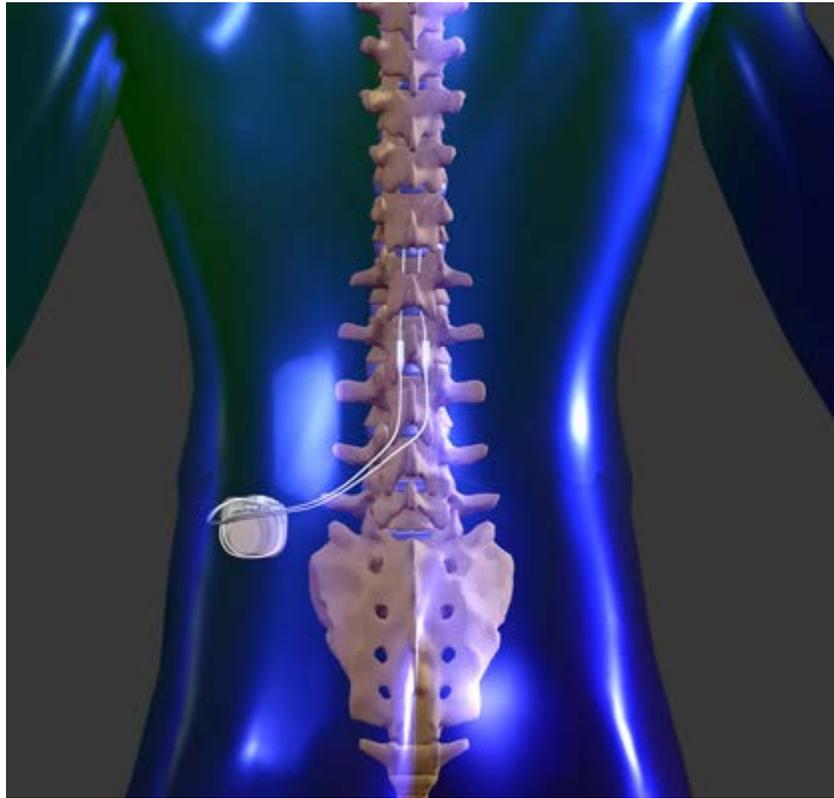
5.1.8.1 Spinal Cord Stimulation

SCS is usually employed later in treatment trajectories, after conventional pain therapies have proved ineffective. It involves placement of electrodes percutaneously in the epidural space or implantation of a surgical paddle lead via laminectomy.³² Spinal cord stimulators are composed of a rechargeable or non-rechargeable battery powered pulse generator, a lead wire with multiple electrodes, and a handheld remote control (Figure 2). Radiofrequency coupled systems include a radiofrequency receiver and an external battery, these systems are designed for higher output levels over sustained and longer periods of time.^{33,34} Units without rechargeable batteries need to be replaced every 2-5 years and those with rechargeable batteries last for 8-25 years.³⁵ Battery life can vary depending on frequency and intensity of use.³⁵ A trial implantation is usually performed and if successful the device will be permanently implanted.³⁶

Traditionally, pain suppression in SCS was achieved through replacement of the sensation with paresthesia, a burning or prickling sensation associated with tingling numbness. Some patients find paresthesia to be unpleasant, especially in movement. Investigation related to intensity and frequency of stimulation has led to development of burst³⁷ and high frequency 10 kHz (HF10) paresthesia free stimulation.³⁸ Dorsal root ganglion SCS was also developed as a more targeted stimulation therapy, however it is currently not approved for use in Canada .

SCS is used to treat a number of chronic pain conditions. Persistent postoperative neuropathic pain, as seen in FBSS is one such condition. Chronic back pain with or without radicular or referred pain can be treated with various surgeries. For example, disk herniation pain can require a discectomy. Following surgery, some patients experience continuing chronic pain of the back, which is labelled as FBSS.³⁹ Another pain condition treated with SCS is complex regional pain syndrome (CRPS). CRPS involves pain due to nerve dysfunction, with (type I) or without (type II) nerve injury. The pain is often felt in one limb.⁴⁰

Figure 2. Implanted Spinal Cord Stimulator



Chronic inoperable limb ischemia, painful diabetic neuropathy, and refractory angina are also conditions that can be treated with SCS. Limb ischemia results from poor perfusion of a limb. Chronic limb ischemia can result in severe pain, limb ischemia and ulcers. When revascularization and other operations are not possible, SCS is a potential alternative treatment to control pain and reduce symptoms.⁴¹

Diabetic neuropathy is a condition resulting from diabetes mellitus. High blood sugar levels can damage the nervous system resulting in chronic neuropathic pain. Most frequently this nerve damage occurs in the legs and feet.⁴² Angina is chest pain resulting from restricted blood flow to the heart. Angina is considered refractory if it persists following medication, angioplasty and bypass surgery.⁴³

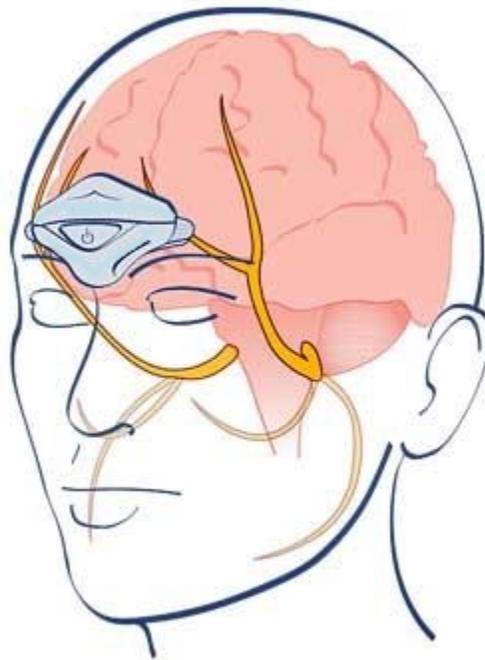
Pain due to cancer can also be treated with SCS. Cancer pain can be due to numerous causes such as tumor progression and invasion, systemic treatments, surgery, infections, and cancer related sedentariness. Nerve compression via neural fibromas or tumor placement can occur, as can ischemia resulting in ischemic pain. Inflammatory and neuropathic pain mechanisms may also play a role in cancer pain.⁴⁴

Complications of SCS include hardware related events, such as lead migration, lead fracture, or lead failure; and biological complications such as infection and pain over the implant.⁴⁵ There are also programming or therapy complications such as loss of paraesthesia, and painful or unpleasant paraesthesia.⁴⁵

5.1.8.2 Transcutaneous Electrical Stimulation of the Supraorbital Nerve

TENS involves placement of electrodes at the site of pain or at a pressure point. The electrodes adhere to the skin and administer electrical current transcutaneously. The TENS unit is battery operated and remote controlled with the ability to modulate pulse frequency, width, and intensity. TENS can be employed as a non-invasive treatment of a number of peripheral pain conditions. TENS stimulation of the supraorbital nerve is employed for pain conditions such as supraorbital neuralgia and chronic migraines or headaches.⁴⁶ The supraorbital nerve is a terminal branch of the frontal nerve and is located in the forehead region above the eyebrows. It gives off neurofilaments to the eyelids. A headband-like electrical stimulator device may be used in TENS of the supraorbital nerve (Figure 3).

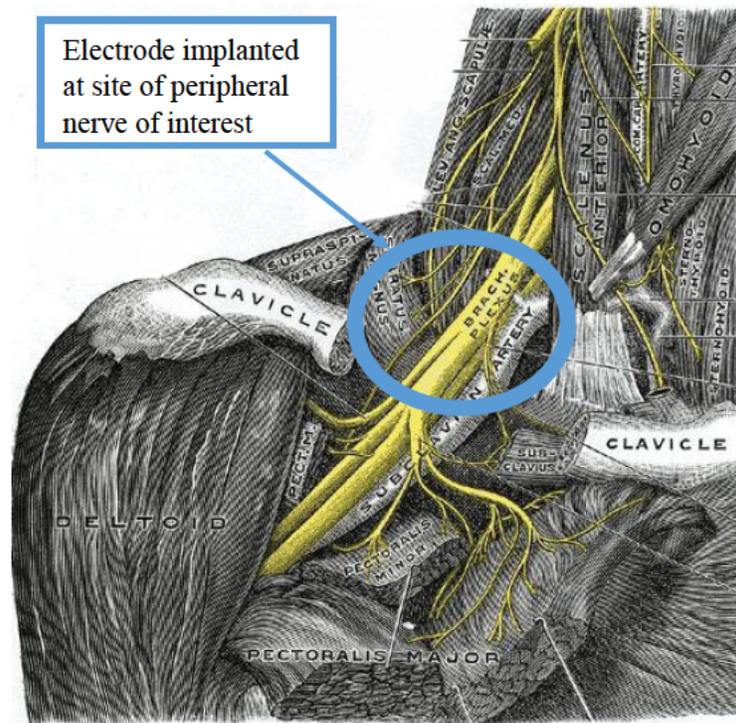
Figure 3. Transcutaneous Electrical Stimulator Applied Over the Site of the Supraorbital Nerves



5.1.8.3 Peripheral Nerve Stimulation and Peripheral Nerve Field Stimulation

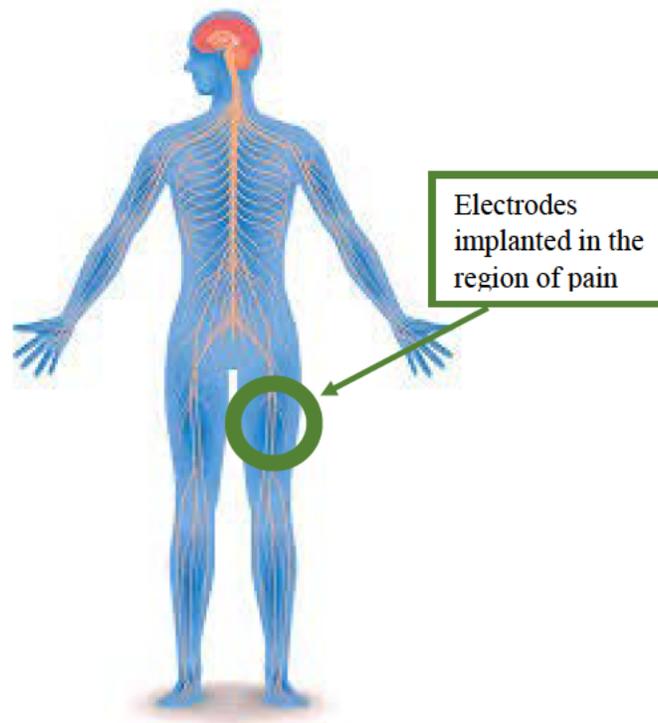
PNS has been used for the treatment of neuropathic pain for over 40 years.⁴⁷ Improvements in surgical techniques and technology resulting in less invasive and more effective procedures has led to a recent increase in its use in refractory pain cases.⁴⁸ PNS involves surgical implantation of an electrode at the site of a peripheral nerve causing pain. This implantation can be achieved through percutaneous placement so as to be sufficiently close to stimulate the peripheral nerve of interest, or through direct placement over the nerve of interest (Figure 4). Peripheral nerves are located outside of the brain and spinal cord. Similar to SCS, a PNS device includes a pulse generator, a lead wire with an electrode, and a handheld remote control. Radiofrequency coupled systems also exist. A trial implantation is performed and if successful followed with a permanent implantation. PNS is indicated for use in chronic pain management following failure of conventional pain therapies and less invasive neuromodulatory therapies such as TENS. Complications associated with PNS and PNfS are similar to those associated with SCS.⁴⁵

Figure 4. Peripheral Nerve Stimulation Example



PNfS is very similar to PNS and has been used to treat a variety of neuropathies. In PNfS the leads are implanted in the subcutaneous tissue in the area of focalized pain (Figure 5). This stimulates the dermatomal distribution of nerve fibers as opposed to any single nerve target. Stimulation is thus delivered within the peripheral field of a peripheral nerve.⁴⁹ PNfS units are similar to those used in PNS and a successful trial must be completed for prolonged use of the technology.

Figure 5. Peripheral Nerve Field Stimulation Example



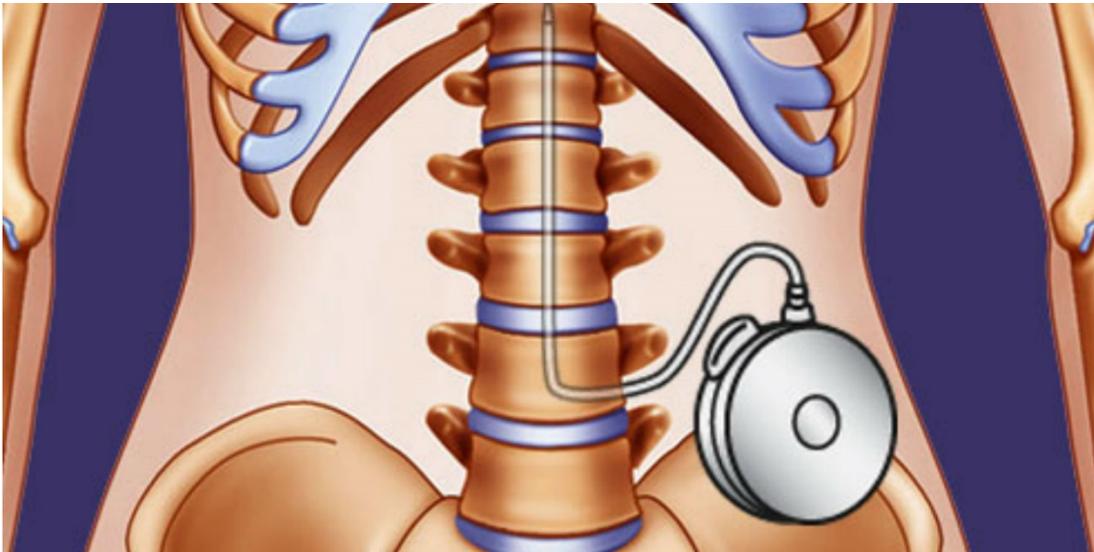
5.1.9 Intrathecal Drug Pump

Intrathecal pumps are employed in a number of cancer and non-cancer pain conditions. An intrathecal pump is a device that delivers medication directly to the cerebrospinal fluid (CSF) into the intrathecal space which surrounds the spinal cord. The device is composed of a pump with a drug reservoir and a catheter that connects the pump to the intrathecal space. The reservoir needs to be replenished every 1-3 months. The pump is approximately the size of a hockey puck and is implanted under the skin of the abdomen (Figure 6).

Pumps can deliver medication continuously or in a customized fashion. In order to customize the rate of administration and dosage a programmable pump is required.⁵⁰ Due to the direct application of the medication the required dose is decreased compared to oral medication. As with the neurostimulatory devices, a trial is required to be successfully completed prior to permanent implantation of the pump. A multitude of medications may be used in pain management via intrathecal pumps. The type, mix, and order of medications administered depends on the individual and the type of pain they are experiencing. Potential medications include opioids, local anesthetics, and adrenergic agonists among others.⁵¹

Complications associated with intrathecal pumps include: bleeding, neurologic injury, catheter complications such as fracture and subsequent leakage, or the development of an inflammatory mass at the tip of the catheter.⁵¹ In as many as 20% of patients with an intrathecal drug delivery system in place, cerebral spinal fluid leaks may occur.⁵¹

Figure 6. Implanted Intrathecal Pump



5.1.10 Conclusions

Chronic pain is a limiting illness with a variety of treatment options. Neuromodulation is an emerging option for patients. There are multiple technologies included in neuromodulation each targeting a different chronic pain presentation and using different implanted stimulators.

Understanding which technologies work best for what kinds of patients is required to further support evidence-based policies and practice.

6 Review of Neuromodulation Guidelines and Best Practice Recommendations

Summary

- A review of guidelines and best practice recommendations identified twenty two relevant documents published between 1993 and 2017 from Canada, the United States, the United Kingdom, Australia, and various international groups.
- Two main considerations were assessed within the guidelines and recommendations: patient selection and risk management.
- Overlap exists between guideline recommendations with some key disagreements in patient selection.

6.1 Purpose

To synthesize current guidelines and best practice recommendations on neuromodulation interventions for treatment of chronic pain.

6.2 Methods

A grey literature search using Google and Google Scholar was performed on June 14, 2018. The following terms were searched: neuromodulation guidelines; TENS supraorbital guidelines; spinal cord stimulation guidelines; peripheral nerve stimulation guidelines; peripheral nerve field stimulation guidelines; intrathecal pumps guidelines. Additionally, a sample of websites from well-known organizations including the National Guidelines Clearing House, Canadian Medical Association, British Columbia Ministry of Health, Best Practice Advocacy Centre New Zealand, the Regulation and Quality Improvement Authority (RQIA; formerly GAIN), Institute for Clinical Systems Improvement (ICSI), National Health and Medical Research Council, and the National Institute for Health Care Excellence (NICE) were searched. Individual guidelines identified through the clinician interviews and the HTA, clinical effectiveness, and patient perspectives systematic reviews were also included for review.

For inclusion guidelines were required to pertain to a relevant neuromodulatory technology and its employment in chronic cancer or non-cancer pain. The full guideline needed to be available and published in the English or French.

6.3 Findings

A guideline review of implantable neurostimulation devices was published in 2014⁵². The inclusion of guidelines was broader than that defined for this review, but was used as an initial summary of the literature. Of the identified guidelines within this review, four met the inclusion criteria for the current report pertinent to SCS⁵³⁻⁵⁶ and two met the inclusion criteria for general neuromodulatory interventions.^{34,57}

The updated search identified 21 guidelines. Of these, four were duplicate guidelines captured in the 2014 review. Thus a total of 22 relevant guidelines were identified and considered: seven pertaining to spinal cord stimulation, seven pertaining to intrathecal pump implants, three pertaining to PNS and PNfS, and five pertaining to general neuromodulation.

A summary of all guidelines and recommendations follows (Table 3).

Two Canadian guidelines were identified. The guidelines were published in 2007 and 2012 and both contain information pertinent to SCS. Six United States of America (USA) guidelines, four United Kingdom (UK) guidelines, and one Australian guideline were identified. Eight of the identified guidelines were produced through international collaboration.

The guidelines and recommendations identified addressed two main considerations: Patient Selection and Risk Management. All recommendations and guidelines included review of the literature and based on evidentiary support of safety and efficacy provided statements regarding patient selection and risk management.

6.3.1 Patient Selection

6.3.1.1 SCS

Patient selection is recommended based on a number of elements. Prognostic factors, pain type, previous treatments, and contraindications help inform if a patient might benefit from SCS. Mailis and Taenzer's 2012 guideline was the only Canadian guideline that considered this process.⁵⁷ Their task force reviewed relevant literature to produce evidence based guidelines for neuropathic pain treatments alternative to pharmacotherapy. One of the treatment modalities assessed by this task force was SCS. Their review returned differing levels of evidentiary support for different pain conditions. Patients with CRPS I & II and FBSS returned B-level recommendation supporting SCS therapy indication. Traumatic neuropathy and brachial

plexopathy returned C-level recommendation supporting SCS therapy indication. Other neuropathic pain conditions returned I-level recommendation supporting SCS therapy indication.

International guidelines included recommendations from EFIC in 1998, EFNS in 2007, NACC in 2014, and EAN in 2016.^{32,34,58,59} All guidelines recommended specific pain conditions and types as indications for SCS therapy. EFIC and NACC identified neuropathic pain and mixed pain conditions as indications. NACC outlined common chronic pain conditions and their recommendations and EFIC included additional specific pain condition recommendations for SCS treatment indications. EFNS and EAN reviewed evidentiary support for SCS treatment in particular pain conditions. EFNS returned B-level recommendation supporting SCS therapy indication in FBSS and CRPS I. Positive confirmatory evidence requiring confirmatory trials was returned for a number of other pain conditions. EAN returned weak evidentiary support for SCS therapy indication in a number of conditions including CRPS I. This is in contrast with the Canadian guideline's recommendations for CRPS I and the EFNS and NAAC guidelines.

The remaining six guidelines also identified specific pain conditions and types indicated for SCS therapy. These guidelines were produced by NICE in 2008, BPS in 2009, NTAC in 2010, North and Shipley's team in 2007, Atkinson's team in 2011, and Sitzman and Provenanzo's team in 2017.^{53-56,60,61} Four included neuropathic pain, FBSS, and CRPS I and or II as indicated pain conditions and types. Three recommended ischemic pain for SCS therapy with one of those noting weaker evidentiary support. One listed ischemic pain as a contraindication for SCS therapy. All indicated some conditions could benefit from SCS therapy on case by case basis given careful screening and selection. Four guidelines identified contraindications to treatment including contraindications to surgery, active or untreated psychiatric or substance abuse disorders, and cognitive impairment impeding consent or self-management post implantation. Four guidelines also recommended the use of multidisciplinary teams in the assessment and management of patients throughout the rehabilitative process.

6.3.1.2 Intrathecal Pumps

No Canadian guidelines pertaining to intrathecal pump for chronic pain management were identified. Of the eight identified guidelines pertinent to intrathecal pump therapy in chronic pain management four were developed through international collaboration.^{58,62-68} Seven of the eight guidelines identified cancer pain as an indication for intrathecal pump therapy and six of the

eight identified some chronic non-cancer pain conditions indicated for treatment. Of those that identified non-cancer pain indications a mixture of neuropathic, nociceptive, and mixed pain conditions were identified. Three guidelines recommended failure or intolerance to less invasive pain management techniques prior to patient selection for intrathecal pump therapy. Five guidelines recommended successful completion of trial for patient selection for treatment. Three guidelines also recommended careful screening including multidisciplinary teams to assess psychological, environmental, and social factors pertinent to patient selection.

6.3.1.3 PNS/PNfS

No Canadian guidelines pertinent to PNS or PNfS control of chronic pain were identified. Six relevant guidelines were identified four of which were developed through international collaboration.

NICE's guidance on PNfS for chronic low back pain identified limited evidence on efficacy and safety.⁶⁹ AHRQ's guideline on occipital nerve stimulation for refractory occipital neuralgia returned a level III recommendation. The EHF's position statement on neuromodulation of headaches found the quality of evidence was limited and recommended further research.⁷⁰ The EFIC consensus statement on neuromodulation of pain identified neurogenic pain and CRPS II as indications for PNS therapy.⁵⁸ The EFNS guidelines and NACC's consensus statement did not draw any conclusions on PNS therapy in chronic pain due to heterogeneity of the clinical literature and general lack of evidence suggesting further research is required.^{32,34}

6.3.1 *Risk Management*

6.3.1.1 SCS

Patient safety and outcomes rely on the support and planning of their care teams. Risk management holds an important role in ensuring optimal outcomes and prevention of harm. One Canadian guideline on risk management of SCS was identified. Kumar and team created recommendations on avoiding complications in SCS therapy.⁷¹ Through review of the literature and consensus amongst an expert panel incidence, severity, reversibility, and net impact of complications were assessed. Based on this review and discussion recommendations pertaining to patient positioning; imaging; percutaneous and surgical lead choice, anchoring, and insertion; intraoperative stimulation; screening trial, stimulation settings, infection control, and pulse generator positioning were developed.

Five other guidelines pertaining to risk management in SCS therapy were identified.^{53,55,58,60,61} One was created through international collaboration. Careful screening and infection prevention were emphasized in two of the guidelines. Four emphasized the need for proper device selection, maintenance, and modification of parameters to best suit each patient's situation. Three guidelines outlined implantation recommendations and holistic rehabilitative care through multidisciplinary teams managing general and special precautions.

6.3.1.2 Intrathecal Pumps

No Canadian guidelines considering risk management for intrathecal pump therapy in chronic pain were identified. Seven guidelines from other countries were identified with five resulting from international collaborations.⁶²⁻⁶⁸ All guidelines considered the safety of intrathecal therapy and response to adverse events and complications such as infection and catheter migration. Five of the guidelines emphasized continuing care concerns recommending appropriate device maintenance and patient follow-up and education. Four of the guidelines outlined pharmacological considerations in terms of dosage, drug of choice, and modifications or adjustments. Two of the guidelines had recommendations pertaining to device and catheter placement for risk management and four guidelines included special considerations for subpopulations of patients such as geriatrics, those undergoing chemotherapy, and those with psychiatric disorders and other comorbidities.

6.4 Conclusions

Of the 22 guidelines considered two were created by Canadian groups and both pertained to SCS. Eight internationally collaborative guidelines were identified pertaining to SCS, intrathecal pumps, and PNS. The guidelines spanned publication dates of 1993-2017 and some built off one another. There was a fair amount of heterogeneity in the PNS/PNfS guidelines owing to the fact that they were more targeted to specific nerve stimulations for specific pain conditions as opposed to more generalized treatment and indications. A commonality amongst the PNS/PNfS guidelines was the authors' indications that more research is required. There was substantial overlap in concepts for risk management for SCS and intrathecal pump therapy. The level of detail for particular considerations and the focus of the guidelines did vary though. The overlap in patient selection between guidelines was also quite high, some controversy seemed to surround support of specific pain condition indications such as CRPS I in SCS

Table 3. Neuromodulation Guidelines and Best Practice Recommendations Summary

Authors and Date	Affiliation	Country	Support, Funding, and Sponsorship	Neuromodulatory Intervention	Pain Indications	Type of Guidelines
Kumar et al. 2007 ⁷¹	Expert Panel	Canada	Non-financial support from Medtronic International Trading SA	SCS	Peripheral neuropathy, back pain, CRPS	Addresses patient positioning; appropriate imaging; lead choice, suturing, and implantation; intraoperative stimulation; stimulation settings; infection control; generator positioning
North and Shipley 2007 ⁵³	Expert Panel	United States	NTAC; NANS	SCS	FBSS, CRPS I & II, peripheral neuropathic pain, phantom limb syndrome, post-herpetic neuralgia, root injury, & spinal cord injury/lesion	Addresses indications; outcomes; prognostic factors; patient selection; risk management; delivery and quality of SCS; cost effectiveness
Ades et al. 2008 ⁵⁴	NICE	United Kingdom	Public Body	SCS	Chronic neuropathic pain and ischemic pain (research trials)	Evidence appraisal of patient selection and intervention effectiveness and safety
Simpson et al. 2009 ⁵⁵	BPS	United Kingdom	BPS, SBNS, and the Neuromodulation Society of UK and Ireland	SCS	FBSS, CRPS, neuropathic pain, ischemic pain	Evidence appraisal of clinical effectiveness in pain conditions
NTAC 2010 ⁵⁶	NTAC	United States	Device company sponsorship	SCS	Chronic neuropathic pain	Position statement on application and effectiveness
Atkinson et al. 2011 ⁶⁰	Australian Neurostimulation	Australia	Medtronic Australasia Pty	SCS	Neuropathic and ischemic	Addresses patient selection; care timing; benefits and complications

	Working Group		Ltd.		pain- indications with varying levels of supporting evidence	
Sitzman and Provenzano 2017 ⁶¹	Best Practices Summary	United States	None	SCS	Chronic pain, neuropathic pain, FBSS, CRPS I & II, chronic refractory angina, ischemic pain, chronic cancer pain	Best practices statement on patient selection; complication mitigation; SCS modality selection
Krames 1993 ⁶²	US Cancer Pain Relief Committee	United States	Medtronic Inc.	Intrathecal Drugs	Cancer pain, non-malignant pain	Guidance on patient selection; problem management; trials
Deer et al. 2010 ⁶³	Consensus Group Guidelines	United States	Medtronic Inc., Inset Technologies, other device sponsorships	Intrathecal Drugs	Chronic non-cancer pain	Guidance on comprehensive patient selection
Deer et al. 2011 ⁶⁴	Consensus Group Guidelines	United States	Inset Technologies	Intrathecal Drugs	Chronic cancer and palliative pain	
Deer et al. 2012 ⁶⁵	Polyanalgesic Consensus Recommendations	International	Medtronic Inc., Azure Pharma Ltd.	Intrathecal Drugs	Neuropathic pain, nociceptive pain, mixed pain	Guidance on comprehensive patient selection
Prager et al. 2013 ⁶⁷	Expert Panel Best Practice Consensus	International	Medtronic Inc.	Intrathecal Drugs	Chronic intractable pain, severe chronic pain	Consensus statement updating algorithms of for intrathecal analgesic use in chronic pain

Eldabe et al. 2015 ⁶⁸	BPS	United Kingdom	Medtronic Inc.	Intrathecal Drugs	Chronic non-malignant pain, cancer pain	Best practices statement on safety; risks and benefits
Deer et al. 2016 ⁶⁶	Update: Polyanalgesic Consensus Recommendations	International	INS, Medtronic Inc., Jazz Pharmaceuticals Inc.	Intrathecal Drugs	Refractory pain	Consensus statement on pain care algorithms; patient selection
NICE 2013 ⁶⁹	NICE	United Kingdom	Public Body	PNfS	Chronic low back pain	Evidence evaluation of efficacy and safety
Sweet et al. 2015 ⁷²	AHRQ NGC	United States	Congress of Neurological Surgeons, American Association of Neurological Surgeons	Occipital Nerve Stimulation (PNS)	Refractory occipital neuralgia	Evidence informed recommendations on use of ONS in occipital neuralgia patients
Martelletti et al. 2013 ⁷⁰	Expert Group on Neurostimulation of Chronic Headaches of European Headache Federation	European International	Device company sponsorships	Occipital Nerve Stimulation (PNS)	Chronic headache	Position statement on efficacy, safety, and technical considerations for ONS
Gybels et al. 1998 ⁵⁸	Consensus Statement EFIC	European International	Medtronic Inc.	General (SCS, PNS, Intrathecal drugs)	Neurogenic pain, mixed pain, intractable angina pectoris, peripheral vascular disease, nociceptive pain	Consensus statement on efficacy and safety of neuromodulatory interventions and effective patient selection
Crucchi et al. 2007 ³⁴	EFNS	European International	Medtronic Inc.	General (PNS, SCS)	Neuropathic pain	Guideline for neuromodulatory interventions and their evidence supported pain indications
Mailis and Taenzer 2012 ⁵⁷	CPS	Canada	CPS	General (SCS)	CRPS I, FBSS, traumatic	Recommendations for SCS patient selection

					neuropathy, brachial plexopathy, other neuropathic pain syndromes	
Deer et al. 2014 ³²	Neuromodulation Appropriateness Consensus Committee	International	INS, Medtronic Inc., St. Jude Medical, Boston Scientific Corp., Nevro Corp., Spinal Modulation Inc.	General (SCS, PNS, PNfS)	Neuropathic pain, mixed pain	Consensus statement on safe and effective application of neuromodulatory interventions
Cruccu et al. 2016 ⁵⁹	EFNS, EAN	European International	EFNS, EAN	General (SCS)	Neuropathic pain, fibromyalgia, CBLP, CRPS I	Guideline on neurostimulation efficacy and safety based on evidence review

7 Review of Health Technology Assessments

Summary

- Of 101 identified citations, 13 studies were included in this review: 10 HTAs, one accelerated systematic review, one rapid review, and one dossier summary with response.
- Evidence on effectiveness of the different types of neuromodulation was mixed, resulting in a range of recommendations for the different neuromodulation types.
- Four HTAs out of five identified in this review that assessed SCS recommended the use of SCS for specific indications of non-cancer pain only.
- Recommendations for the use of intrathecal pumps were mixed; four HTAs gave positive recommendations regarding their use while three indicated that the evidence did not support the use of intrathecal pumps as compared to alternative treatment options.
- Only one HTA assessed transcutaneous supraorbital nerve stimulation (tSNS) and one HTA assessed PNS and PNfS, making it difficult to draw strong conclusions about their clinical effectiveness.
- Cost impacts were only identified for SCS and intrathecal pumps.

7.1 Purpose

To synthesize health technology assessments or reassessments on neuromodulation.

7.2 Methods

7.2.1 Search Strategy

A systematic review was completed. The HTA Database was searched from inception until March 15th, 2018. Terms aimed to capture the neuromodulation technologies of interest such as “neuromodulation,” “spinal cord stimulation,” “electric stimulation,” “intrathecal drug administration” were combined with the Boolean Operator “or.” These searches were then combined with terms to indicate pain such as “pain clinics,” “pain,” “chronic pain,” and “intractable pain.” Terms were searched as text words in titles and abstracts or as subject headings (e.g. MeSH). The search strategy was developed by a research librarian. No filters or limitations were used. The full search strategy can be found in Appendix A.

In addition, grey literature and the websites of known HTA organizations were searched. This grey literature search was guided by the Canadian Agency for Drugs and Technologies in Health’s “Grey Matters.”

7.2.2 Study Selection

Abstracts retrieved were screened in duplicate. All abstracts selected for inclusion by either reviewer proceeded to full-text review. Abstracts were excluded if they did not meet the inclusion criteria, if full-text was not available, or if the study was not available in English or French.

Studies included after the first screen were read in full-text by two reviewers. Studies were included in the review if they met all inclusion criteria and failed to meet any exclusion criteria in Table 4. Publications were considered to be a relevant HTA if they included a systematic review of clinical effectiveness of any of the neuromodulation technologies of interest, including HTAs that also included a systematic review of cost-effectiveness. Any discrepancy between reviewers' inclusions was resolved through discussion between reviewers or a third reviewer.

Table 4. Inclusion and Exclusion criteria HTA Review

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Health Technology Assessment on one (or more) of the following neuromodulation technologies: <ul style="list-style-type: none"> ○ Spinal cord stimulation of cancer or non-cancer pain ○ Transcutaneous supraorbital nerve stimulation for non-cancer pain ○ Peripheral nerve stimulation for non-cancer pain ○ Peripheral nerve field stimulation for non-cancer pain ○ Intrathecal pump for cancer or non-cancer pain • English or French language only • Any outcomes • Adult population (18 years and older) 	<ul style="list-style-type: none"> • Not a Health Technology Assessment <ul style="list-style-type: none"> ○ Does not include systematic review of clinical effectiveness • Does not assess any of the neuromodulation technologies of interest • Not available in English or French • Does not use adult population as patient cohort

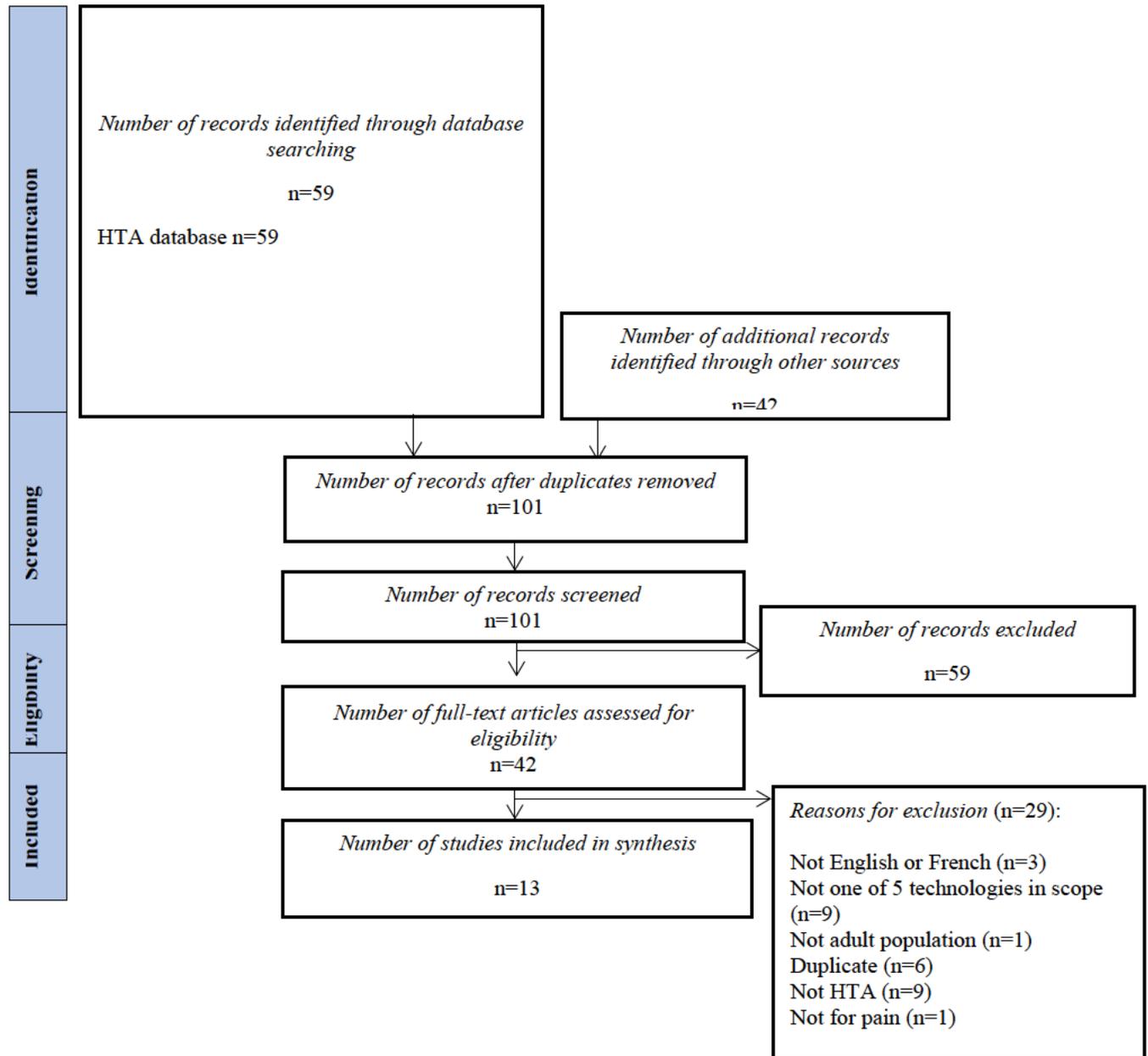
7.2.3 Data Extraction

Data were extracted and synthesized for all HTAs included in this review. Extracted data included: characteristics (author/date, country, study objectives, data collection methods, amount and type of evidence included), details on clinical effectiveness, cost-effectiveness and *de novo* models included in each HTA, and recommendations. Discrepancies between reviewers during data extraction were resolved through consensus.

7.3 Results

Abstract review was completed in duplicate for 101 identified publications (Figure 7). Of the abstracts reviewed, 59 were excluded and 42 proceeded to full text review. Full text review resulted in the inclusion of 13 studies. Studies were excluded if they: were not published in English or French (n=3); did not assess any of the neuromodulation technologies of interest (n=9); did not assess adult patients with chronic pain (n=2); were not HTAs (n=9); were duplicate records (n=6). Data are narratively synthesized in the results below. The clinical effectiveness and cost effectiveness results from these HTAs is also highlighted in the narrative summary, in addition to identification of any gaps within the broad clinical area

Figure 7. HTA Study Inclusion Flow Chart



7.3.1 Study Characteristics

A total of 13 studies were included in this review (Table 5). These included ten HTAs, one accelerated systematic review, one rapid review, and one dossier summary with response.

Four studies were from Canada,^{56,73-75} four were from the UK,^{69,76-78} two were from the USA,^{79,80} and one study each was from Ireland,⁸¹ Belgium⁸² and Australia.⁸³ All studies assessed clinical effectiveness and safety of the neuromodulation type(s) being assessed. Eight of these also assessed costs impacts of the technologies.^{69,73,74,76,79,80,82,83} One HTA conducted a *de novo* model to evaluate cost-effectiveness.⁶⁹

Ten studies assessed neuromodulation therapies for patients with non-cancer pain only. Of these, four assessed SCS,^{69,80,81,84} and four assessed intrathecal pump.^{74,75,79,83} One study assessed tSNS⁷⁸ and one study assessed PNS and PNfS.⁷⁷ Two studies assessed neuromodulation for both cancer and non-cancer patient cohorts; one for SCS and intrathecal pump⁸² and one for intrathecal pump.⁷⁶ One study assessed intrathecal pumps for patients with cancer pain only.⁷³

Table 5. Characteristics of Included Health Technology Assessments and Other Forms of Evidence Synthesis

Organization, Country, Year	Technology and Population	Type of Report	Research Question/Objective	Clinical Effectiveness Systematic Review	Cost-effectiveness Systematic Review
Health Information and Quality Authority, Ireland, 2013	Spinal Cord Stimulation: Non-cancer Pain	HTA	To evaluate the appropriateness and potential impact of introducing clinical referral or treatment thresholds for implantation of a spinal cord stimulation device	<p>Databases: Cochrane Library databases, CRD databases, PubMed.</p> <p>Search dates: Unknown until May 2013</p> <p>Primary outcomes: Not reported</p>	-
KCE, Belgium, 2012	Spinal Cord Stimulation: Non-cancer Pain and Cancer Pain	HTA	Assess clinical effectiveness, safety, cost-effectiveness of spinal cord stimulation (SCS).	<p>Databases: EMBASE (through Ovid), PubMed (through MEDLINE), Cochrane Library</p> <p>Search dates: Jan-Feb 2012, for literature from 2002 onward</p> <p>Primary outcomes: Satisfactory pain relief (through patient reported pain measurement scales)</p>	<p>Databases: Centre for Reviews and Dissemination database, Cochrane Database of Systematic Reviews, websites of HTA institutes listed on INAHTA website</p> <p>Search dates: Searched to 18 June, 2012</p> <p>Primary outcomes: Costs</p>
	Intrathecal Pump: Non-cancer Pain and Cancer Pain	HTA	Assess clinical effectiveness, safety, cost-effectiveness of intrathecal analgesic delivery pumps (IADPs).	<p>Databases: EMBASE (through Ovid), PubMed (through MEDLINE), Cochrane Library</p> <p>Search dates: Jan-Feb 2012, for literature from 2002 onward</p> <p>Primary outcomes: Satisfactory pain relief (through patient reported pain measurement scales)</p>	<p>Databases: Centre for Reviews and Dissemination database, Cochrane Database of Systematic Reviews, websites of HTA institutes listed on INAHTA website</p> <p>Search dates: Up to 18 June, 2012</p> <p>Primary outcomes: Costs</p>

NICE, UK, 2009	Spinal Cord Stimulation: Non-cancer Pain	HTA	To assess the clinical and cost-effectiveness of spinal cord stimulation in the management of chronic neuropathic or ischemic pain.	<p>Databases: Medline, EMBASE, Cochrane Library</p> <p>Search dates: From inception to 2007. Searches conducted Aug – Sep 2007.</p> <p>Primary outcomes: Pain, health-related quality of life (HRQoL) and adverse effects</p>	<p>Databases: Medline, EMBASE, Cochrane Database of Systematic Reviews, NHS Centre for Review and Dissemination databases</p> <p>Search dates: From inception to 2007. Searches conducted Aug – Sep 2007.</p> <p>Primary outcomes: Costs</p>
Ontario Health Technology Assessment Series, Canada, 2005	Spinal Cord Stimulation: Non-cancer Pain	HTA	To determine the effectiveness of spinal cord stimulation to manage chronic intractable neuropathic pain and evaluate the adverse events and Ontario-specific economic profile of this technology.	<p>Databases: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, INHATA</p> <p>Search dates: 2000-January 2005</p> <p>Primary outcomes: Pain relief (Secondary: functional status, quality of life, and procedural complications)</p>	-
Washington State Health Care Authority, United States, 2010	Spinal Cord Stimulation: Non-cancer Pain	HTA	To critically appraise and analyze research evidence on the effectiveness of and complications related to the use of spinal cord stimulation in patients with chronic neuropathic pain and to the extent possible, consider the potential financial impact.	<p>Databases: PubMed, EMBASE, CINAHL, ClinicalTrials.gov, CRISP, HSTAT, The Cochrane Library, EconLit, PsychINFO, AHRQ, INAHTA</p> <p>Search dates: Inception-February 2010</p> <p>Primary outcomes: Pain intensity and pain relief</p>	<p>Databases: EconLIT, NHS Economic Evaluation Database, CADTH, Centers for Medicare and Medicaid Services, FDA, Institute for Clinical Systems Improvement, National Guideline Clearinghouse</p> <p>Search dates: Inception-February 2010</p>
ASERNIP-S, Australia,	Intrathecal Pump: Non-cancer Pain	Accelerated systematic	Assess safety and efficacy of implantable infusion devices for chronic pain	<p>Databases: MEDLINE, PRE-MEDLINE, EMBASE, Current</p>	<p>Databases: MEDLINE, PRE-MEDLINE, EMBASE,</p>

2003		review	and spasticity	Contents, PubMed Search dates: – up to April 2003 Primary outcomes: Safety and efficacy (including VAS, Ashworth scale).	Current Contents, PubMed Search dates: – up to April 2003 Primary outcomes: Costs data
INESSS, Canada 2013	Intrathecal Pump: Non-cancer Pain	HTA	To assess the evidence on efficacy, safety, and cost effectiveness of intrathecal pumps in chronic non-cancer pain with the aim of developing better guidelines of patient selection, clinical interventions, and post implantation follow-up in patient groups of interest.	Databases: Medline through PubMed, Embase, Cochrane Library, CINAHL, HTA through the Centre for Reviews and Dissemination, Guidelines International Network, and the AHRQ National Guideline Clearinghouse Grey Lit search strategy-appendix A Search dates: Efficacy and safety: 2007-August 2011. Clinical Guidelines: 2000-August 2011 Primary outcomes: Efficacy and safety (through patient reported pain measurement scales including VAS and numerical rating scale, McGill Pain Questionnaire, QoL and function), and organizational/clinical guidelines	Databases: Medline through PubMed, Embase, Cochrane Library, CINAHL, HTA through the Centre for Reviews and Dissemination, Guidelines International Network, and the AHRQ National Guideline Clearinghouse Grey Lit search strategy-appendix A Search dates: Costing- 2007-August 2011 Primary outcomes: Cost effectiveness
New York Department of Health, US, 2015	Intrathecal Pump: Non-cancer Pain	Dossier Summary and Response	Assess effectiveness, harms and costs of implantable infusion pumps for non-cancer pain	Dossier of evidence provided by manufacturer (details of selection not provided) Additional Search for Evidence was done by Assessors – Databases: Included Hayes, Inc., Cochrane Library, NICE, Blue Cross/Blue Shield HTA Program, the Veterans Administration Technology Assessment Program, BMJ Clinical	Dossier of evidence provided by manufacturer (details of selection not provided) Additional Search for Evidence was done by Assessors – Databases: Included Hayes, Inc., Cochrane Library, NICE, Blue Cross/Blue Shield HTA

				<p>Evidence, CADTH, Washington State HTA Program, United States Preventive Services Task Force, and AHRQ. US FDA MAUDE database</p> <p>Search dates: 1946 – October 2015</p> <p>Primary outcomes: Pain measures, Quality of Life and disability measures, intake of oral pain medications</p>	<p>Program, the Veterans Administration Technology Assessment Program, BMJ Clinical Evidence, CADTH, Washington State HTA Program, United States Preventive Services Task Force, and AHRQ. US FDA MAUDE database</p> <p>Search dates: 1946 – October 2015</p> <p>Primary outcomes: Costs</p>
NICE, United Kingdom, 2000	Intrathecal Pump: Non-cancer Pain and Cancer Pain	HTA	Collect available evidence on use of intrathecal pump systems to draw conclusions on the effectiveness, side-effects, and cost-effectiveness of the different systems in use, and to compare with existing treatments.	<p>Databases: MEDLINE, EMBASE, Cancer CD, PubMed</p> <p>Search dates: Not reported</p> <p>Primary outcomes: Efficacy measures (including VAS, McGill Pain Questionnaire, ability to return to work), side-effects.</p>	<p>Databases: MEDLINE, EMBASE, Cancer CD, PubMed</p> <p>Search dates: Not reported</p> <p>Primary outcomes: Costs</p>
OHTAC, Canada, 2016	Intrathecal Pump: Non-cancer Pain	HTA	To investigate the benefits, harms and cost-effectiveness and budget impact of intrathecal drug delivery systems compared with current standards of care for adult patients with chronic pain owing to nonmalignant (noncancer) conditions.	<p>Databases: MEDLINE, Embase, Cochrane Library databases, NHS Economic Evaluation Database, and Tufts Cost-Effectiveness Analysis Registry</p> <p>Search dates: January 1994 to March 2014 for systematic reviews; January 1994 to April 2014 for primary studies</p> <p>Primary outcomes: Patient benefit (pain relief, physical function, emotional benefit), drug-</p>	<p>Databases: MEDLINE, Embase, Cochrane Library databases, NHS Economic Evaluation Database, and Tufts Cost-Effectiveness Analysis Registry</p> <p>Search dates: January 1994 to April 2014</p> <p>Primary outcomes: Not listed</p>

				related harms, procedure-related harms, equipment related harms, all serious events, overall patient judgement (including treatment satisfaction and health-related quality of life).	
OHTAC, Canada, 2016	Intrathecal Pumps: Cancer pain	HTA	To investigate the benefits, harms and cost-effectiveness and budget impact of intrathecal drug delivery systems compared with current standards of care for adult patients with chronic pain owing to malignant (cancer) conditions	<p>Databases: MEDLINE, Embase, Cochrane Library databases, NHS Economic Evaluation Database, and Tufts Cost-Effectiveness Analysis Registry</p> <p>Search dates: January 1994 to March 2014 for systematic reviews; January 1994 to April 2014 for primary studies</p> <p>Primary outcomes: Patient benefit (pain relief, physical function, emotional benefit), drug-related harms, procedure-related harms, equipment related harms, all serious events, overall patient judgement (including treatment satisfaction and health-related quality of life).</p>	<p>Databases: MEDLINE, Embase, Cochrane Library databases, NHS Economic Evaluation Database, and Tufts Cost-Effectiveness Analysis Registry</p> <p>Search dates: January 1994 to April 2014</p> <p>Primary outcomes: Not listed</p>
NICE, 2015, United Kingdom	Transcutaneous electrical stimulation of Supraorbital nerve: Non-Cancer Pain	Rapid Review	None Listed	<p>Databases: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library, PubMed and BLIC</p> <p>Search dates: Inception – July 28, 2015</p> <p>Primary outcomes: Efficacy and safety</p>	-
NICE,	Peripheral nerve	HTA	1) To carry out a	Databases: Cochrane library,	

United Kingdom, 2012	(and Peripheral nerve Field Stimulation: Non-Cancer Pain		<p>comprehensive search of published and unpublished literature</p> <ol style="list-style-type: none"> 2) To summarize the evidence 3) To evaluate the strength and weakness of evidence on efficacy and safety related to each type of nerve stimulation procedure for each type of refractory pain 4) To produce an evidence map 	<p>Cochrane central register of controlled trials, ZETOC, Current controlled trials metaregister</p> <p>Search dates: Inception – March/April 2012</p> <p>Primary outcomes: None listed</p>	
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7.3.2 *Clinical Effectiveness and Safety*

Findings on clinical effectiveness and safety were identified for each of the five neuromodulation types assessed in this HTA (Table 5).

7.3.2.1 Spinal Cord Stimulation: Non-cancer Pain

Of the five HTAs that assessed the clinical effectiveness and safety for SCS for non-cancer pain, four stated that the primary outcomes assessed for effectiveness were satisfactory pain relief.

^{69,80,82,84} Primary outcomes were not reported for one HTA.⁸¹

A 2013 report by HIQA found evidence to support the use of SCS for FBSS and CRPS,⁸¹ however this report also included two earlier HTAs that were also found in this assessment.^{69,82} Two other HTAs also found evidence to support the use of SCS for FBSS and CRPS,^{80,84} The HIQA report also found low quality evidence that SCS is effective for other neuropathic pain, including complex regional pain type 2, post-herpetic neuralgia, phantom limb pain, partial spinal cord injury, chronic low back pain, and chronic back and limb pain.⁸¹ One 2012 HTA found limited evidence of efficacy for FBSS, CRPS, critical limb ischemia (CLI), and refractory angina pectoris.⁸² A 2009 NICE study concluded that SCS was effective for pain of neuropathic origin but not ischemic origin.⁶⁹ Several of the studies reported that the evidence identified was largely of low to moderate quality.

Safety was assessed in three reports.^{80,82,84} Adverse events were reported to be rare.⁸² Various technical problems were reported due to the components of the technology, including lead problems and implantable pulse generator problems. Other complications identified included infection and dural puncture.

7.3.2.2 Spinal Cord Stimulation: Cancer Pain

One HTA sought to identify evidence of clinical effectiveness for SCS for cancer pain, however it did not identify any relevant evidence that fulfilled its criteria.⁸²

7.3.2.3 Transcutaneous Supraorbital Nerve Stimulation: Non-cancer Pain

A NICE report⁷⁸ found two RCTs, two case series and an adverse event report on the clinical effectiveness and safety of tSNS. Primary outcomes included pain intensity and change in mean number of migraine days per month. The RCT found statistically significant reduction in the mean number of migraine days suffered per month (baseline 6.94 days to 4.88 days after three months) after treatment. Pain intensity did not show statistically significant reduction.

7.3.2.4 Peripheral Nerve Stimulation (PNS) and Peripheral Nerve Field Stimulation: Non-cancer Pain

One HTA⁷⁷ assessing the clinical effectiveness of PNS and PNFS identified 22 RCTs. The outcomes investigated were diverse and included pain, analgesic use, headaches, function, quality of sleep, depression, patient satisfaction, quality of life, and adverse effects. The pooled mean difference in pain reduction when comparing PNS/PNFS to sham was statistically significant. Overall, serious adverse events were uncommon for case studies (reports included lead migration, infection and device malfunction). This HTA concluded that evidence on PNFS for chronic low back pain is limited in quantity and quality, and duration of follow-up is limited. Evidence on safety is also limited. The resulting recommendation was this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

7.3.2.5 Intrathecal Pump: Non-cancer Pain

Six HTAs sought to assess the clinical effectiveness and safety for intrathecal pump for non-cancer pain. Primary outcomes included patient pain relief and other patient benefits, procedure-related harms, all serious events, and overall patient judgement (including quality of life).

A 2016 study concluded that current evidence neither rules out nor establishes the superiority of intrathecal pumps for managing non-cancer pain.⁷⁴ Three HTAs determined that there was evidence to suggest that intrathecal pumps are effective for non-cancer pain,^{75,79,83} however two of these note that the evidence was weak or poor quality.^{75,79} One HTA by NICE in 2000 determined that, while the evidence found suggested that intrathecal pump therapy shows analgesic benefits, the authors did not find evidence that it was superior to existing treatments,

such as injections or oral medications.⁷⁶ One HTA found no relevant evidence that fulfilled its criteria.⁸²

Safety and adverse events were evaluated in four HTAs.^{74,76,79,83} A UK study⁷⁶ found that risks included pharmacological side-effects (reported in 3-26% of patients) and mechanical side-effects (reported in up to 25% of patients). One USA HTA⁷⁹ found that, while adverse effects were not consistently reported among studies, common device-related complications included pump failure, reoperation due to pump or catheter headache, and headache. Less common problems included infection, seroma, granuloma, and catheter migration. An Australian study determined that pumps appear safe but both drug-related and device-related complications have been reported.⁸³ One HTA stated that comparative evidence of harms was not found.⁷⁴

7.3.2.6 Intrathecal Pump: Cancer Pain

Clinical effectiveness and safety of intrathecal pumps for cancer pain was assessed in three HTAs. One Belgian HTA⁸² found limited evidence of efficacy of intrathecal pumps for refractory cancer pain, while one Canadian HTA⁷³ determined that current evidence could not establish the benefit of intrathecal pumps compared with current standards of managing pain. A NICE HTA⁷⁶ also concluded that they did not identify evidence to show that intrathecal pump is superior to other analgesic treatments available. All three HTAs found the evidence to be of low quality.

The Belgian HTA⁸² found low quality evidence that there was no difference in the frequency of serious adverse events between patients receiving intrathecal pump treatment and those receiving conventional care for pain from cancer. The Canadian study⁷³ did not find adverse events meeting the criteria of the review to be reported in any studies.

Table 6. Clinical Effectiveness and Safety Findings

Technology and Population	Organization, Country, Year	Evidence Identified	Findings	Conclusions
Spinal Cord Stimulation: Non-cancer pain (N=5)	Health Information and Quality Authority, 2013 Ireland	Clinical guidelines (n=6), Health Technology Assessments (n=3), systematic reviews (n=2)	<ul style="list-style-type: none"> Clinical practice guidelines recommend SCS for failed back or complex regional pain syndrome (type 1) One guideline suggest it should be delivered through multidisciplinary pain management team Evidence suggests that SCS is more effective than continued conservative management or repeat operation Poor quality evidence that SCS is effective for other neuropathic pain: complex regional pain type 2, post-herpetic neuralgia, phantom limb pain, partial spinal cord injury, chronic low back pain, chronic back and leg pain, ischemic limb pain, angina pain. 	“Spinal cord stimulation has been shown to be an effective additional treatment to conservative management for individuals with failed back surgery and complex regional pain syndrome.”
	KCE, Belgium, 2012	RCTs (n=8), Systematic reviews (n=2)	<ul style="list-style-type: none"> Low to moderate quality of evidence for effectiveness of SCS in patients with failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), critical limb ischemia (CLI) and refractory angina pectoris. Serious adverse events appear to be rare. 	“The available data provide only limited evidence for efficacy or cost effectiveness of neuromodulation. For SCS, the indications that are best documented are failed back surgery syndrome, complex regional pain syndrome, critical limb ischemia and angina pectoris.”
	NICE, UK, 2009	RCTs (n=11)	<ul style="list-style-type: none"> 2 RCTs looked at SCS and failed back surgery syndrome. One RCT found SCS had a greater effect than conventional medical management at 12 months (34% had 50% pain relief at 12 months versus 7% in the CMM group). Another also reported statistically significant benefit for pain relief. One RCT found SCS in combination with physical therapy was more effective than physical therapy alone 4 RCTs looked at SCS and ischemic pain conditions. Two studies reported pain relief and 	“Evidence suggested that SCS was effective in reducing the chronic neuropathic pain of FBSS and CRPS type I. For ischemic pain, there may need to be selection criteria developed for CLI, and SCS may have clinical benefit for refractory angina in the short term.”

			<p>neither found statistically significant pain relief</p> <ul style="list-style-type: none"> 4 RCTs looked at SCS and angina – one reported pain outcomes and found no statistically significant difference. 	
	Ontario Health Technology Assessment Series, 2005, Canada	Health Technology Assessments (n=6), Randomized controlled trials (n=2), Non-randomized controlled trials (n=2)	<ul style="list-style-type: none"> All 6 health technology assessments concluded there is evidence to support the effectiveness of SCS for managing neuropathic pain; quality ranged from very weak to moderate Level 2 evidence from 1 study and level 3a evidence from one study supports the use of SCS for neuropathic limb pain from failed back syndrome Level 2 evidence from 1 study supporting the use of SCS for neuropathic limb pain associated with complex regional pain syndrome Most common technical failures were lead problems (10.8%), and implantable pulse generator problems (10.2%) Most common procedural complications were infection (1.2%) and dural puncture (1.2%) 	“Level 2 evidence from 2 studies of high quality supports the effectiveness of SCS to reduce pain in some neuropathic pain conditions. There is supportive evidence from secondary outcomes from level 3a evidence that treatment with SCS improves functional status and QOL [quality of life].”
	Washington State Health Care Authority, United States, 2010	<p><i>Effectiveness:</i> RCTs (n=3), prospective cohort (n=1)</p> <p><i>Safety:</i> Case studies (n=6)</p>	<ul style="list-style-type: none"> RCTS reported significantly improved outcomes in short-term for SCS patients over control patients but results were mixed at 5 year follow-up Prospective cohort study found no difference in outcomes between patients in the SCS and control groups Found short-term revision to SCS components common; 10-21% of patients required electrode repositioning, 4-9% required electrode replacement, 1-36% required revision or replacement of generator, 3-4% required removal due to infection 	“Patients randomized to receive SCS had significantly improved pain relief compared to those randomized to undergo control treatments in two RCTs with <2 year follow-up.”
Spinal Cord Stimulation: Cancer pain (n=1)	KCE, Belgium, 2012	None found	-	-
Int rat he cal Pu m	ASERNIP-S, Australia,	RCT (n = 1) Case studies (n = 6)	<p>Safety:</p> <ul style="list-style-type: none"> The RCT found that total number of complications 	“Infusion of opioid agents for treatment of chronic pain or

	2003		<p>was not greater in the patients receiving intrathecal pump treatment vs. patients receiving conventional pain care.</p> <p>Efficacy:</p> <ul style="list-style-type: none"> • Significant reductions in pain (measured using VAS) for both intrathecal pump therapy and conventional pain care patients. Greater reduction in pain scores for patients receiving drug therapy but no statistical difference. • Greater reduction in toxicity scores for patients receiving intrathecal drug therapy. • Report did not assess quality of evidence. 	<p>baclofen for treatment of spasticity ... appears effective for patients who have been screened for response to intrathecal medication prior to implantation. This method of treating chronic pain or spasticity appears safe, although drug related complications do occur ... but device related complications ... can also occur which may result in surgical revision or removal of the device.”</p>
	INESSS, Canada, 2013	<p>Systematic reviews (n=5), Prospective case studies (n=2), Clinical guidelines (n=4)</p>	<p>Efficacy:</p> <ul style="list-style-type: none"> • Weak evidence (mostly observational studies) - efficacy in neuropathic, nociceptive, and mixed pain, particularly in postsurgical refractory lumbosciatica. Significant clinical reduction (>50%) in pain in at least 30% of patients, a non-negligible proportion of patients (7-10.5%) discontinue treatment due to insufficient pain reduction. • Due to weak evidence unable to conclude if there is improvement in quality of life. • Use of intrathecal pump was associated with decreased use of oral medication. <p>Safety:</p> <ul style="list-style-type: none"> • Side effects are frequent, complications can require reoperation or pump removal. 6.3-8.9% of patients withdraw from treatment due to adverse effects. <p>Clinical and Organizational Guidance:</p> <ul style="list-style-type: none"> • patient group composed of nociceptive, neuropathic, and mixed pain patients. Before implantation, psychological assessment should be completed. A multidisciplinary team with at least one pain specialist, one psychologist and one nurse specialist is required 	<p>Based on weak evidence intrathecal pumps are effective at significant pain reduction in approximately 40% of patients. Many non-lethal and non-serious side effects and complications arise, 6-9% of patients discontinue treatment due to safety effects.</p>
	KCE, Belgium,	None found		-

	2012			
	New York Department of Health, US, 2015.	Systematic reviews (n=12) RCTs (n=4) Cohort studies (n=17) Case studies (n=4)	<p>Pain outcome measures</p> <ul style="list-style-type: none"> All SRs reported clinically and statistically reductions in pain (using VAS or numeric scales) 1 RCT reported on pain, patients with dose reduction (vs. control) had significantly elevated pain; 70% of dose reduction group patients dropped out. 7 cohort studies: all found statistically significant and clinically meaningful average reduction in pain <p>QoL, Disability outcome measures</p> <ul style="list-style-type: none"> Several cohort studies reported improvements in QoL indicators, including mood, sleep, general activity; 5 cohort studies reported improvements in functionality and disability scores, 2 SRs noted improved function in the observational studies they summarized. <p>Oral Pain Medications</p> <ul style="list-style-type: none"> 1 SR reported reduction in complementary pain medications used among patients treated with intrathecal drug therapy; In 1 prospective cohort study that required patients to wean off opiates at enrollment, average daily intake of oral opiate reduced from 128mg morphine daily to 4mg morphine daily (sustained over 36 months). <p>Harms</p> <p>Various adverse effects were reported (not consistently) among studies.</p>	<p>“There is a fairly consistent body of poor quality evidence drawn mostly from fair to poor quality observational studies demonstrating short- and long-term clinically significant (greater than or equal to 30%) reductions in pain in patients with chronic non-cancer pain treatment with intrathecal drug therapy.”</p> <p>“Common device-related complications include pump failure, reoperation due to pump or catheter failure, and headache. Infection, seroma, granuloma, and catheter migration are reported less frequently.”</p>
	NICE, UK, 2000 [Cancer and non-cancer pain]	Case series studies (n=53)	<p>Evidence found was deemed suboptimal due to lack of comparator data.</p> <ul style="list-style-type: none"> In the 16 studies on VAS <u>before-and-after</u> use: average scores declined from 7.6/10 to 3/10. Various QoL indicators reported positive effects from use of intrathecal pump. 	<p>“All the case series and reports that evaluated intrathecal opioid treatments showed analgesic benefit but we found no evidence that this form of therapy is superior to existing analgesic treatments such as tablets or injections.”</p>

			Risks included pharmacological side-effects (reported in 3-26% of patients) and mechanical side-effects (reported in up to 25% of patients).	
	OHTAC, Canada, 2016.	Cohort studies (n=2)	<p>1 retrospective cohort study (for failed back surgery syndrome) found that:</p> <ul style="list-style-type: none"> • Intrathecal pumps significantly reduced pain and morphine consumption compared to oral opioid analgesia alone or a program of analgesia plus rehabilitation. • However, pumps were not superior in patient-reported well-being or quality of life. • There is no evidence of superiority of intrathecal pumps over oral opioids in global pain improvement and global treatment satisfaction. • Comparative evidence of harms was not found. 	“Current evidence does not establish (or rule out) superiority or cost-effectiveness of intrathecal drug delivery systems for managing chronic refractory nonmalignant pain.”
Intrathecal Pumps: Cancer pain (n=3)	KCE, Belgium, 2012	RCT (n=1)	<ul style="list-style-type: none"> • Evidence was low to moderate quality. • Low quality evidence of effectiveness for IADP in patients with chronic refractory cancer pain. • Serious adverse events appear to be rare. 	“The available data provide only limited evidence for efficacy or cost effectiveness of neuromodulation... For IADP the best documented indication is refractory cancer pain.”
	NICE, United Kingdom, 2000 [Cancer and non-cancer pain]	Case series (n=53)	<ul style="list-style-type: none"> • Evidence found was deemed suboptimal due to lack of comparator data. • Two distinct patient types were identified: those with long life expectancy but resistant pain; and cancer patients with limited life expectancy and intractable pain resistant to all other treatments. <ul style="list-style-type: none"> • In the 16 studies on VAS <u>before-and-after</u> use: avg scores declined from 7.6/10 to 3/10. • Various QoL indicators reported positive effects from use of programmable infusion pump. • Risks included pharmacological side-effects (reported in 3-26% of patients) and mechanical side-effects (reported in up to 25% of patients). 	“All the case series and reports that evaluated intrathecal opioid treatments showed analgesic benefit but we found no evidence that this form of therapy is superior to existing analgesic treatments such as tablets or injections.”

	OHTAC, Canada, 2016.	RCT (n=1), Case series (n=1)	<ul style="list-style-type: none"> Evidence was deemed to be very low quality. 1 RCT of patients treated with intrathecal pumps showed significant improvements in pain and toxicity scores vs. patients treated with conventional pain care, measured using VAS. Adverse events meeting criteria of the review not reported in any studies. 	“Current evidence could not establish the benefit, harm, or cost-effectiveness of intrathecal drug delivery systems compared with current standards of care for managing refractory cancer pain in adults.”
Transcutaneous electrical stimulation of Supraorbital nerve: Non-Cancer Pain	National Institute for Health and Care Excellence, 2015, United Kingdom	Randomized controlled trial (n=1) Case series (n=2) FDA adverse event report (n=1)	<ul style="list-style-type: none"> RCT found statistically significant reduction in number of migraine days from baseline (6.94 days) to 3 months (4.88 days) after treatment. Pain intensity was not statically significantly reduced. Case series found statistically significant reduction in migraine days per month from 4.5 at baseline to 2.06 at 60 days post-treatment. Found statistically significant reduction in average pain intensity during migraine. 4% of patients in case series of 2,313 reported adverse event that was minor and reversible 	-
Peripheral Nerve Field Stimulation: Non-Cancer Pain	National Institute for Health and Care Excellence, 2012, United Kingdom	Randomized Control Trials (n=22) Case studies with more than 10 participants (n=60)	<ul style="list-style-type: none"> Pooled mean difference in pain reduction was statistically significant comparing PNS/PNFS and sham at 3.08 (95% CI: 2.51-3.65) 	-

7.3.3 Cost Effectiveness

Eight HTAs assessed costs impacts of the technologies.^{69,73,74,76,79,80,82,83} One of these conducted a *de novo* model to evaluate cost-effectiveness⁶⁹ (Table 7). Costs impacts were only identified for SCS and intrathecal pumps.

7.3.3.1 Spinal Cord Stimulation: Non-cancer Pain

Three HTAs conducted economic evaluations of SCS for non-cancer pain. Two HTAs assessed economic evidence for SCS for non-cancer pain through systematic reviews. One of these⁸² identified four cost-utility analyses, two cost-effectiveness studies, three studies that conducted both cost-effectiveness and cost-utility analyses, and five cost-consequences analyses. It concluded that, although the available evidence seemed to indicate that SCS could be cost-effective at the referred thresholds for FBSS and CRPS, the low quality of evidence did not allow clear conclusions to be made. The available evidence was inconclusive for cost-effectiveness related to patients with angina.

One US HTA⁸⁰ identified three cost-utility analyses for SCS in patients with FBSS. The assessment found there was some evidence that SCS combined with conventional medical management of pain is cost-effective at moderate ICER levels (below £20,000 per QALY) compared with conventional medical management alone or reoperation. Another cost-utility model assessed found SCS would improve utility with an ICER of €45,819 per QALY gained, compared to conventional medical management.

A UK HTA⁶⁹ performed a *de novo* economic evaluation on the cost-effectiveness of SCS for treating FBSS and CRPS, using a two-stage model. The model consisted of a decision tree to six months, followed by a Markov process extending to 15 years. FBSS and CRPS conditions were modelled using data from two trials of FBSS and one trial of CRPS. For FBSS, the ICERs for SCS in combination with conventional medical management (assuming device longevity of 4 years and using a device price figure of £9000) were £10,480 per QALY gained compared with conventional medical management alone, and £9219 per QALY gained compared with repeat operation. For CRPS, SCS in combination with conventional medical management produced an

ICER of £32,282 per QALY gained (assuming device longevity of 4 years and using a device price of £9000) when compared to conventional medical management alone.

7.3.3.2 Intrathecal Pump: Non-Cancer Pain

One of the four HTAs assessing costs of intrathecal pumps for patients with non-cancer pain found some evidence that intrathecal pumps may be less costly in the long term than conventional medical management for chronic pain and spasticity.⁸³ A US HTA⁷⁹ identified modelling studies that indicate the use of intrathecal pumps leads to long-term saving and cost-utility analyses that report ICERs within well-accepted willingness to pay thresholds (US\$50,000 to US\$100,000). Another HTA⁷⁶ also found some evidence that intrathecal pumps may provide some cost-benefit compared to conventional analgesic therapy, however this study included mixed cohorts with patients suffering from cancer pain and non-cancer pain. One Canadian HTA⁷⁴ determined that the evidence on cost-effectiveness was of insufficient quality to assess the appropriateness of funding intrathecal pumps publicly. This study found the budget impact of funding intrathecal pumps in Ontario to be between \$1.5 and \$5 million per year.

7.3.3.3 Intrathecal Pump: Cancer Pain

Three HTAs assessed costs of intrathecal pumps for patients with cancer pain.^{73,76,82} One Belgian HTA found evidence that intrathecal pumps show positive results compared to usual care but noted that data on cost-effectiveness was weak.⁸² A Canadian HTA found that current evidence could not establish the cost-effectiveness of intrathecal pumps for managing cancer pain in adult patients compared to current standards of care.⁷³ It determined that the cost of publicly funding intrathecal pumps in Ontario for cancer pain would result in a budget impact between \$100,000 and \$500,000 per year. One UK study assessed costs for patients with cancer and non-cancer pain and found some evidence that intrathecal pumps may provide some cost-benefit compared to conventional analgesic therapy.⁷⁶

Table 7. Cost-effectiveness Systematic Review Findings

Technology and Population	Organization, Country, Year	Evidence Identified	Findings	Conclusions
Spinal Cord Stimulation: Non-cancer Pain (n=3)	KCE, Belgium, 2012	Cost-utility analyses (n=4), Cost-effectiveness studies (n=2), Cost-effectiveness and cost-utility (n=3), Cost-consequences analyses (n=5)	<ul style="list-style-type: none"> • One trial-based study comparing SCS to re-operation over 3.1 years (for FBSS) reported positive results towards SCS with a 72% probability of being cost-effective at a threshold of US\$ 40,000. • One other trial-based study for a FBSS cohort presented inconclusive results with SCS in combination to “usual” care being more costly but also offering important improvements in patients’ EQ-5D scores over time when compared to “usual” care alone. • Three decision analytic models supported the cost-effectiveness of SCS for FBSS; two of these reported robust results at a threshold of GBP 20,000 (probability of SCS being cost effective of ≥89% and ≥82% versus CMM and re-operation respectively at this threshold), while the remaining study showed that SCS was dominant over a patient’s lifetime (both cheaper and more effective). • Three studies for CRPS displayed positive results for SCS (one was an RCT, two were decision analytic models over a 15-year life span comparing SCS to CMM, which reported ICERs of GBP 3,562 per QALY and GBP 25,095 per QALY respectively, for their base-case scenarios). 	“Although the available evidence in failed back surgery syndrome and complex regional pain syndrome, overall, appears to indicate that SCS could be cost-effective at the referred thresholds... the low quality of the evidence does not allow making clear conclusions. In patients with refractory angina pectoris the available evidence on cost-effectiveness was inconclusive and for patients with CLI no evidence on cost-effectiveness was available.”
	NICE, UK, 2009	Cost-effectiveness study (n=1)	<ul style="list-style-type: none"> • The study identified used a two-stage model (decision tree and Markov model) to compare SCS and conventional care management. <ul style="list-style-type: none"> ○ ICERs for SCS base case at 2 years were £33,053 per QALY. ○ Short-term (2yr) cost-effectiveness ratios ranged £21,908 - £45,816 per QALY 	“In the lifetime analysis, it was found that SCS was dominant (it cost less and accrued more benefits) in both base case and one-way sensitivity analyses.”
	Washington State Health Care Authority, United States, 2010	Cost-utility analysis (n=3)	<ul style="list-style-type: none"> • One model found that SCS would improve utility at a higher cost with a ICER of €45,819 per QALY gained compared to conventional medical management • Another model found for failed back syndrome, SCS and conventional management together had improved outcomes and increased cost compared to either alone, and ICERs were below £20,000/QALY • Another model found SCS dominant over reoperation 	“There is some evidence that SCS added to CMM is cost-effective at moderate ICER levels compared with CMM alone and/or reoperation.”

Spinal Cord Stimulation: Cancer Pain (n=1)	KCE, Belgium, 2012	Not found	-	-
Intrathecal Pump: Non-cancer Pain (n=6)	ASERNIP-S, Australia, 2003	Cost studies (n=3)	<ul style="list-style-type: none"> 1 study (US) estimated direct medical costs of intrathecal morphine therapy for FBSS, vs. conventional care. It found cost-effectiveness for two scenarios (base case: most likely adverse event rate and cost of care; best case: lowest adverse event rate and cost of care at 65% of base case), but not for worst case scenario (highest adverse rate and costs of care at 135% of base rate) 1 UK study performed meta-analysis of literature and info using costs derived from UK hospitals. It estimated that continuous intrathecal infusion with baclofen had acceptable cost/benefit ratio when compared with other funded health interventions. 1 study analyzed cost-effectiveness: compared costs for intrathecal drug therapy for FBSS, compared with conventional care, costs for conventional care were higher (\$38,000 over 5 yrs) vs. intrathecal drug therapy (\$29,410). 	“Treatment of chronic pain via intrathecal opioids and spasticity via intrathecal baclofen may be less costly than medical management in the long-term.”
	INESSS, Canada, 2013	Cost-effectiveness study (n=1), systematic review (n=1)	<ul style="list-style-type: none"> One study reports pumps are cost effective compared to conventional medical management in chronic non-cancer pain. Cost analysis estimated pump implantation cost at 28,340CAD (the device accounting for over half the cost). The 2009-10 cost of 24 implantations estimated at 680,130CAD and at 1,283,613CAD by 2015 including 5% annual increase in implantation, follow-up costs, and constant unit price. Economic burden could be mitigated by decreased pain management interventional need and increased patient productivity 	Good quality economic evaluation. Likely cost-effective although there is potential for growing costs in future.
	KCE, Belgium, 2012	Not found		-
	New York Department of Health, US, 2015.	Cost analyses (n=4), cost-utility analyses (n=3), cost-utility analysis (n=1)	<ul style="list-style-type: none"> Overall, studies report that treatment of non-cancer pain is costly; although intrathecal drug therapy is more expensive than conventional care, it is more effective. ICERs are within accepted willing to pay thresholds (US\$50,000 – US\$100,000). [Report notes that long-term savings are estimated by modelling studies with particular assumptions]. 	“The cost of intrathecal drug therapy is higher than conventional pain therapy in the short-term. However, long-term savings is estimated by modeling studies with particular assumptions. Cost-utility analyses report incremental cost-effectiveness ratios within well-accepted willingness to pay thresholds, however assumptions are based on poor quality

Intrathecal Pump: Cancer pain (n=3)	NICE, United Kingdom, 2000 [Cancer and non-cancer pain]	Cost-minimization analysis (n=1), Cost-effectiveness analysis (n=1), Study assessing actual costs of intrathecal treatment (n=1), Study comparing type 1 pumps with type 5 pumps (n=1)	<ul style="list-style-type: none"> • The cost-minimization analysis modelled costs of 5 different morphine-administration routes. • The cost-effectiveness analysis comparing costs of intrathecal pumps vs. conventional care (for FBSS) found that intrathecal therapy costs were less than conventional therapy costs after 22 months of treatment (US\$82,893 vs. US\$85,186). • The authors stated that it was not possible to determine the actual costs of intrathecal therapy from the study assessing costs <p>- The study comparing costs of type 1 pumps with type 5 pumps found costs for type 5 pumps were initially higher, but after 3 months costs were lower</p>	evidence.” “Very little evidence emerged on the comparative costs of intrathecal pump systems and conventional analgesic therapy. However, a number of cost-modelling projections may indicate some cost-benefit at varying times after the initiation of therapy, depending on individual patient circumstances.”
	OHTAC, Canada, 2016	Cost-minimization analyses (n=2) cost-utility analyses (n=2)	<ul style="list-style-type: none"> • One cost-minimization analysis with a randomized design found pumps were cheaper than conventional pain care over a 5 year period (\$29,410 vs. 38,000) and at least equally effective. Results were not sensitive to changes in certain assumptions. • One cost-minimization analysis (using a computer simulation model) found pumps were cheaper over conventional pain care over a 5 year period (\$82,893 vs. \$85,186) and at least equally as effective. Results were sensitive to changes in certain assumptions. • 1 cost-utility analysis using retrospective chart review data (modelled for 10 year period) found pumps were more effective (QALY gain of 1.15) and more costly (increase of \$13,034), giving an incremental cost per QALY gained of \$11,326 for pumps vs. conventional pain care. • 1 cost-utility analysis found pumps were more effective on an annual basis (QALY gain of 0.31) and more costly (increase of £9,049), leading to incremental cost per QALY gained of £29,030 for pumps vs. conventional care. 	“Cost-effectiveness evidence is of insufficient quality to assess the appropriateness of funding intrathecal drug delivery systems.” “The budget impact of funding intrathecal drug delivery systems would be between \$1.5 and \$5.0 million per year.”
	KCE, Belgium, 2012	Cost-effectiveness study (n=1), Cost-consequences analysis (n=1)	<ul style="list-style-type: none"> • Both studies showed positive results • compared to ‘usual’ care’. • One trial-based evaluation done over a 5-year period showed significantly lower costs for IADP versus “usual” care and better outcomes. • The other study was a modelling exercise which made strong assumptions, therefore the generalizability of its results is a challenge. 	“Mirroring the lack of good evidence on effectiveness found in the literature, data on cost-effectiveness were equally weak.”

	NICE, United Kingdom, 2000	Cost-minimization analysis (n=1) Cost-effectiveness analysis (n=1) Study assessing actual costs of intrathecal treatment (n=1) Study comparing type 1 pumps with type 5 pumps (n=1)	<ul style="list-style-type: none"> • The cost-minimization analysis modelled costs of 5 different morphine-administration routes. • The cost-effectiveness analysis comparing costs of intrathecal pumps vs. conventional care (for FBSS) found that intrathecal therapy costs were less than conventional therapy costs after 22 months of treatment (US\$82,893 vs. US\$85,186). • The authors stated that it was not possible to determine the actual costs of intrathecal therapy from the study assessing costs <p>The study comparing costs of type 1 pumps with type 5 pumps found costs for type 5 pumps were initially higher, but after 3 months costs were lower</p>	“Very little evidence emerged on the comparative costs of intrathecal pump systems and conventional analgesic therapy. However, a number of cost-modelling projections may indicate some cost–benefit at varying times after the initiation of therapy, depending on individual patient circumstances.”
	OHTAC, Canada, 2016	Economic evaluation report (n=1)	<ul style="list-style-type: none"> • Costs of pumps was found to be likely higher than low-cost conventional pain therapy for cancer pain, but lower than high-cost conventional pain therapy if used for long enough duration. • Meta-analysis was not possible due to lack of comparative evidence. 	“Current evidence could not establish the benefit, harm, or cost-effectiveness of intrathecal drug delivery systems compared with current standards of care for managing refractory cancer pain in adults. Publicly funding intrathecal drug delivery systems for cancer pain would result in a budget impact of several hundred thousand dollars per year.”

7.3.4 Recommendations

Eleven of the included HTAs in the systematic review provided recommendations regarding the use of the neuromodulation technologies assessed (Table 8). Four gave specific recommendations on SCS^{69,81,82,84}, one gave recommendations on PNS/PNFS,⁷⁷ and seven gave recommendations on pumps.^{73-76,79,82,83}

7.3.4.1 SCS

All four HTAs providing recommendations on the use of SCS recommended its use for specific indications of non-cancer pain only after lack of success in reducing pain through other treatment options. One Canadian HTA recommended its use in patients with chronic, neuropathic pain for whom standard pain treatments have failed and when there is no indication for surgical intervention to treat the underlying condition.⁸⁴ One UK HTA recommended SCS for adults with pain of neuropathic origin but not ischemic origin, unless in the context of research⁶⁹; the Irish HTA similarly recommended SCS for patients with chronic, intractable neuropathic pain.⁸¹ The Belgian HTA recommended the use of SCS in patients with FBSS, CRPS or angina.⁸²

7.3.4.2 PNS/PNFS

The HTA on PNS and PNfS specified that PNfS should only be used with special arrangements for clinical governance, consent and audit or research.⁷⁷

7.3.4.3 Intrathecal Pump

Recommendations regarding use of intrathecal pumps were mixed. Of the seven HTAs providing recommendations on intrathecal pumps, four gave positive recommendations regarding use^{75,76,82,83} while three indicated that the evidence did not support the use of intrathecal pumps as compared to alternative treatment options.^{73,74,79} Two HTAs recommended the use of intrathecal pumps in patients with chronic non-cancer pain,^{75,83} one recommended its use in patients with cancer pain,⁸² and one recommended its use in patients with either cancer pain or non-cancer pain.⁷⁶

Table 8. HTA Recommendations

Organization	Spinal Cord Stimulation	Peripheral Nerve Stimulation/PNfS	Intrathecal pump
ASERNIP-S (2003) ⁸³			Intrathecal pumps appear effective for patients who have been screened for response to intrathecal therapy prior to implantation.
HIQA (2013) ⁸¹	Recommended for adults with chronic, intractable neuropathic pain if the following conditions are met: (1) Failure to improve symptoms after 6 months of conservative management, (2) physical and psychological assessment (3) successful outcome after trial.		
INESSS (2013) ⁷⁵			Recommended for patients with non-cancer pain
KCE (2012) ⁸²	SCS considered in selected patients FBSS, CRPS, angina pectoris) after an assessment by a multidisciplinary team. Application of SCS in a specific patient should be preceded by a stepwise pain management approach where less invasive treatment options have failed.		Intrathecal pump considered in selected patients with cancer pain after an assessment by a multidisciplinary team. Use of intrathecal pump in a specific patient should be preceded by a stepwise pain management approach where less invasive treatment options have failed.
New York Dept of Health (2015) ⁷⁹			Not possible to conclude what groups would most benefit from or be harmed by intrathecal drug therapy.
NICE (2000) ⁷⁶			Intrathecal pumps for patients with chronic pain (cancer and non-cancer) appear to be beneficial.
NICE (2009) ⁶⁹	SCS recommended for adults with chronic pain or neuropathic origin who: (1) continue to experience chronic pain for at least 6 months despite appropriate medical management and (2) have had a successful trial.		
NICE (2009) ⁶⁹	SCS not recommended as a treatment option for adults with chronic pain of ischemic origin except in the context of research.		
NICE (2012) ⁷⁷		Evidence on PNfS for chronic low back pain is limited in quantity and quality, and duration of follow-up is limited. Evidence on safety is also limited. This procedure should only be used with special arrangements for clinical governance, consent and audit or research.	
NICE (2015) ⁷⁸	None reported		
OHTAC (2005) ⁸⁴	Considered for patients with chronic, neuropathic pain for whom standard pain treatments have failed and when there is no indication for surgical intervention to treat the underlying condition.		

OHTAC (2016) ⁷⁴ [non-cancer]			Very low quality evidence found that demonstrated pumps reduced pain and opioid consumption in patients.
OHTAC (2016) ⁷³ [cancer pain]			Evidence identified could not establish benefit, harm, or cost-effectiveness of intrathecal pumps compared with current standard of care for patients with refractory cancer pain.
Washington State HCA (2010) ⁸⁰	None Reported		

7.4 Conclusions

Thirteen HTAs were included in this systematic review. Studies that were identified in these HTAs included RCTs, systematic reviews, clinical guidelines and case studies that reported on the clinical effectiveness and safety of the five neuromodulation types assessed in this HTA.

Between five HTAs on SCS, there was limited evidence suggesting it is effective for pain of neuropathic origin for specific indications, including FBSS, CRPS, CLI, and angina; however several of the HTAs indicated that evidence on efficacy was generally of low to moderate quality. No evidence was identified on the efficacy of SCS for cancer pain. Considerably fewer HTAs were identified on tSNS, PNS and PnFS for non-cancer pain; those that were identified provided few firm conclusions on efficacy, rendering it difficult to draw conclusions on the appropriate use of these technologies. The most number of HTAs (seven) were included for intrathecal pump, although evidence was mixed regarding its clinical effectiveness when compared to other pain management approaches.

Eight HTAs also assessed the economics of the technologies; studies identified on costs of the neuromodulation types included cost-utility analyses, cost-effectiveness studies, and cost-consequences analyses. Only one *de novo* costs model was identified. Budget impact analyses were only identified for SCS and intrathecal pumps. Broadly, while the available evidence indicates that SCS could be cost-effective for FBSS and CRPS, the low quality of evidence does not allow clear conclusions to be made.

Costs studies assessed the cost effectiveness of intrathecal pumps for non-cancer indications (including chronic pain and spasticity) as well as cancer pain. There is some evidence that pumps may be less costly in the long term than conventional medical management for chronic pain and spasticity, but the evidence on cost-effectiveness was deemed to be generally of low quality.

8 Overview of Updated Systematic Reviews on Neuromodulation

8.1 Purpose

To supplement and update clinical effectiveness and safety findings from the HTA systematic review where necessary.

8.2 Methods

Following review of the available HTA literature, updated or de novo search strategies were developed with the help of a medical librarian for each neuromodulatory technology of interest. The updated searches built upon the most appropriate HTAs identified informed by the databases and timelines searched and the quality of evidence found. A summary of the updated searched is provided in Table 9. Detailed systematic review methodology for each technology is reported in each review's section.

Table 9. Updated Neuromodulation Search Summary

Pain Type	Technology	Timeline	Study Type of Interest
Cancer	SCS	Inception-May 2018	RCT
Non-Cancer	SCS	2013-May 2018	RCT
	PNS/PNfS	2012-May 2018	RCT
	Supraorbital TENS	2015-May 2018	Any
Mixed	Intrathecal Pumps	Inception-May 2018	RCT

8.3 Findings

Detailed findings for clinical effectiveness and safety of the neuromodulatory technologies of interest are provided in the individual review sections following. A Summary of the current identified neuromodulation evidence is presented below (Table 10).

Table 10. Neuromodulation Summary of Evidence

	Chronic Cancer Pain	Chronic Non-Cancer Pain
SCS	N=0	N= 15 RCTs Total number of patients =675* Quality scores: 8 low, 4 high, 3 unclear Primary outcome of pain (any measure)=10/15 Significant Pain Reduction

		Outcome=9/15
PNS	Not included in HTA	N=9 RCTs Total number of patients =323* Quality scores: 8 low, 1 unclear Primary outcome of pain (any measure)=5/6 Significant Pain Reduction Outcome=5/6
PNfS	Not included in HTA	N=1 RCT Total number of patients =116 Quality score: unclear Primary outcome of pain (any measure)=1/1 Significant Pain Reduction Outcome=1/1
Supraorbital TENS	Not included in HTA	N= 1 non-comparative cohort study Total number of patients =23 Quality score = not completed Primary outcome of pain (any measure)=unclear Significant Pain Reduction Outcome=unclear
Intrathecal Pumps	N=4 RCTs Total number of patients = 464* Quality score:1 low, 1 high, 2 unclear Primary outcome of pain (any measure)=3/4 Significant Pain Reduction Outcome=3/4	N=4 RCTs Total number of patients =607* Quality=3 low, 1 unclear ROB Primary outcome of pain (any measure)=3/4 Significant Pain Reduction Outcome=1/4

ROB=Risk of Bias

* Sum of all RCT cohorts

9 Systematic Review of Effectiveness of Spinal Cord Stimulation in Cancer Pain

Summary:

- There were 3,350 records retrieved in the search of which five proceeded to full-text review.
- None of the articles met eligibility criteria thus no articles proceeded to data extraction.
- There is no RCT evidence available assessing the use of SCS in cancer pain.

9.1 Purpose

To synthesize studies on clinical effectiveness of spinal cord stimulation for cancer pain.

9.2 Methods

9.2.1 Search Strategy

A systematic review was conducted. MEDLINE, EMBASE, PsycINFO, the Cochrane Central Register of Controlled Trials and CINAHL were searched from inception to May 2018. The search strategy was developed by a medical librarian. The search strategy combined words associated with spinal cord stimulation, such as “spinal cord stimulation” or “electric stimulation therapy,” with words associated with pain management and cancer pain, such as “pain management,” “cancer pain,” or “intractable pain.” Terms were searched as both text words (title/abstract) and subject headings (e.g. MeSH). Searches were limited to English or French, human studies, and randomized controlled trials. The full search strategy can be found in Appendix B.

9.2.2 Study Selection

RCTs examining SCS for cancer pain were included. All abstracts were reviewed in duplicate. Any abstract included by either reviewer proceeded to full-text review. Studies were excluded if they were not RCTs, were not for cancer pain, used other neuromodulation techniques, or were animal studies. Relevant systematic reviews were searched for potentially relevant articles.

Studies included after abstract review were screened in duplicate. Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion in Table 11. Any discrepancy between reviewers was resolved through discussion and consensus.

Table 11. Inclusion and Exclusion Criteria SCS for Cancer Pain

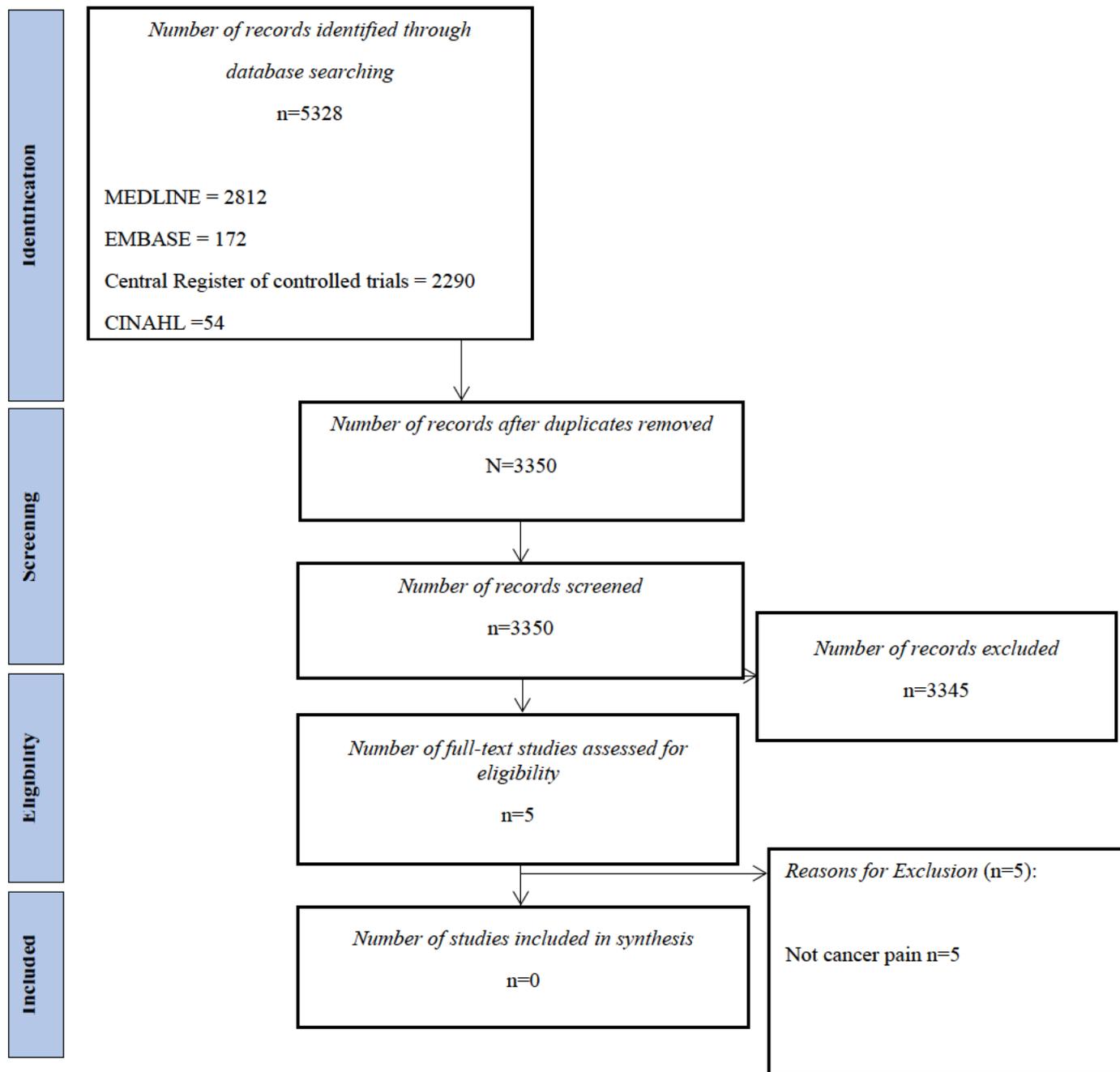
Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Patients undergoing SCS for cancer pain • English or French language only • RCT study design • Adult population • Outcomes of interest: <ul style="list-style-type: none"> ○ Pain assessment (e.g. VAS, McGill Pain Questionnaire) ○ HR QoL ○ AE/SAE ○ Healthcare utilization (e.g. intake of oral pain medication) ○ Patient satisfaction 	<ul style="list-style-type: none"> • Not RCT • Other neuromodulation technologies • Animal studies • Does not report original data • Full text not available

9.3 Results

The searched returned 3,350 titles and abstracts. Five of these proceeded to full text review. None of the articles assessed cancer pain⁸⁵⁻⁸⁹. Zero relevant articles were identified (see Figure 8).

Including results from the previous HTA,⁸² no RCTs assessing SCS for cancer pain were identified.

Figure 8. Study Inclusion Flowchart SCS Cancer Pain



9.4 Conclusions

No RCT evidence was identified for SCS in cancer pain.

10 Systematic Review of the Clinical Effectiveness of Spinal Cord Stimulation in Non-cancer Pain

Summary:

- This review was an update of a previous review conducted by the Health Information and Quality Authority.
- The searched returned 2,724 records, and fifteen randomized controlled trials were included in the final data analysis, including relevant records from the previous review.
- Eight RCTs were of low risk of bias, three were of uncertain risk, and four were high risk of bias.
- Thirteen articles assessed pain using multiple pain measurements. Nine of these reported significant improvements in pain, three reported no significant improvement, and one did not indicate significance.
- Other outcomes included patient's perception of change and perceived change, quality of life, opioid use, limb salvage rates, and exercise capacity. Perceived effect, opioid use, and exercise capacity were significantly improved. There was mixed evidence regarding quality of life and perception of change. There was no improvement in limb salvage rates.

10.1 Purpose

The purpose of this review was to update a review conducted by the Health Information and Quality Authority (HIQA) from 2013 assessing SCS for chronic, non-cancer pain.

10.2 Methods

10.2.1 Search Strategy

This systematic review updated a review conducted in 2013 by HIQA. The initial review searched the Cochrane Library Systematic Review and HTA Databases, the Centre for Reviews and Dissemination databases, and Pubmed with a meta-analysis and review filter applied. Only HTAs or systematic reviews were included. Randomized Controlled Trials (RCTs) were identified via inclusion in the systematic reviews included.

We built upon the HIQA review. MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials were searched from 2013 to May 2018. The search strategy was developed in consultation with a medical librarian. The search strategy combined words associated with SCS, such as “electric stimulation” or “neurostimulation,” with words associated with pain management, such as “pain management,” and specific types of pain, such as “chronic pain.” A Cochrane RCT filter was also applied to improve precision. Terms were searched as both text words (title/abstract) and subject headings (e.g. MeSH). Detailed search strategy is in

Appendix C. The search was limited to human studies. PRISMA guidelines were followed throughout the review.⁹⁰

10.2.1 Study Selection

Studies comparing SCS to placebo for the treatment of chronic non-cancer pain were included (Table 12). Chronic pain was assessed based on the ICD-11 classifications.⁸ Studies were excluded if they failed to meet the inclusion criteria above, if they were animal studies, or if they compared different modes of SCS with no placebo setting (i.e. burst vs. tonic without a placebo setting). Relevant systematic reviews and meta-analyses were not included, but were flagged and reference lists were searched for other potentially relevant articles. All abstracts were reviewed in duplicate. Any abstract included by either reviewer proceeded to full text review. This initial screen was intentionally broad to ensure all relevant literature was captured.

Studies included after abstract review proceeded to full-text review. Full text review was completed in duplicate. Studies were included if they met all inclusion criteria presented in Table 12. Any discrepancy between reviewers was resolved through discussion and consensus. If required, a third reviewer was consulted.

Table 12. Inclusion and Exclusion Criteria SCS Non-cancer Pain

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Pertaining to clinical effectiveness of SCS for chronic non-cancer pain • English or French language only • RCT study design • Adult population • Outcomes of interest: <ul style="list-style-type: none"> ○ Pain assessment (e.g. VAS, McGill Pain Questionnaire) ○ HR QoL ○ AE/SAE ○ Healthcare utilization (e.g. intake of oral pain medication) ○ Patient satisfaction 	<ul style="list-style-type: none"> • Other pain-management techniques • Does not compare to placebo or care as usual • Cancer pain or any other non-chronic pain • Not an RCT • Does not report original data • Animal studies • Not English or French • Published prior to January 1st, 2013

The same inclusion and exclusion criteria were applied to the RCTs identified in the previous HTA to determine eligibility.⁸¹

10.2.2 Data Extraction

Data from the final included studies were extracted by one reviewer using a standard data extraction form, and data were verified by another reviewer. Details of the technology used, information on the intervention, patient characteristics, and primary and secondary outcomes were extracted.

10.2.3 Quality Assessment

During data extraction, quality assessment was completed. Quality was assessed using the Cochrane Tool for Assessing Risk of Bias. Using the Cochrane Risk of Bias tool, each RCT is assessed for seven areas of bias (random assignment generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and any additional potential sources of bias).⁹¹ Each study was assigned “low,” “high,” or “unclear” risk of bias for each of these seven potential sources of bias.

10.2.4 Data Analysis

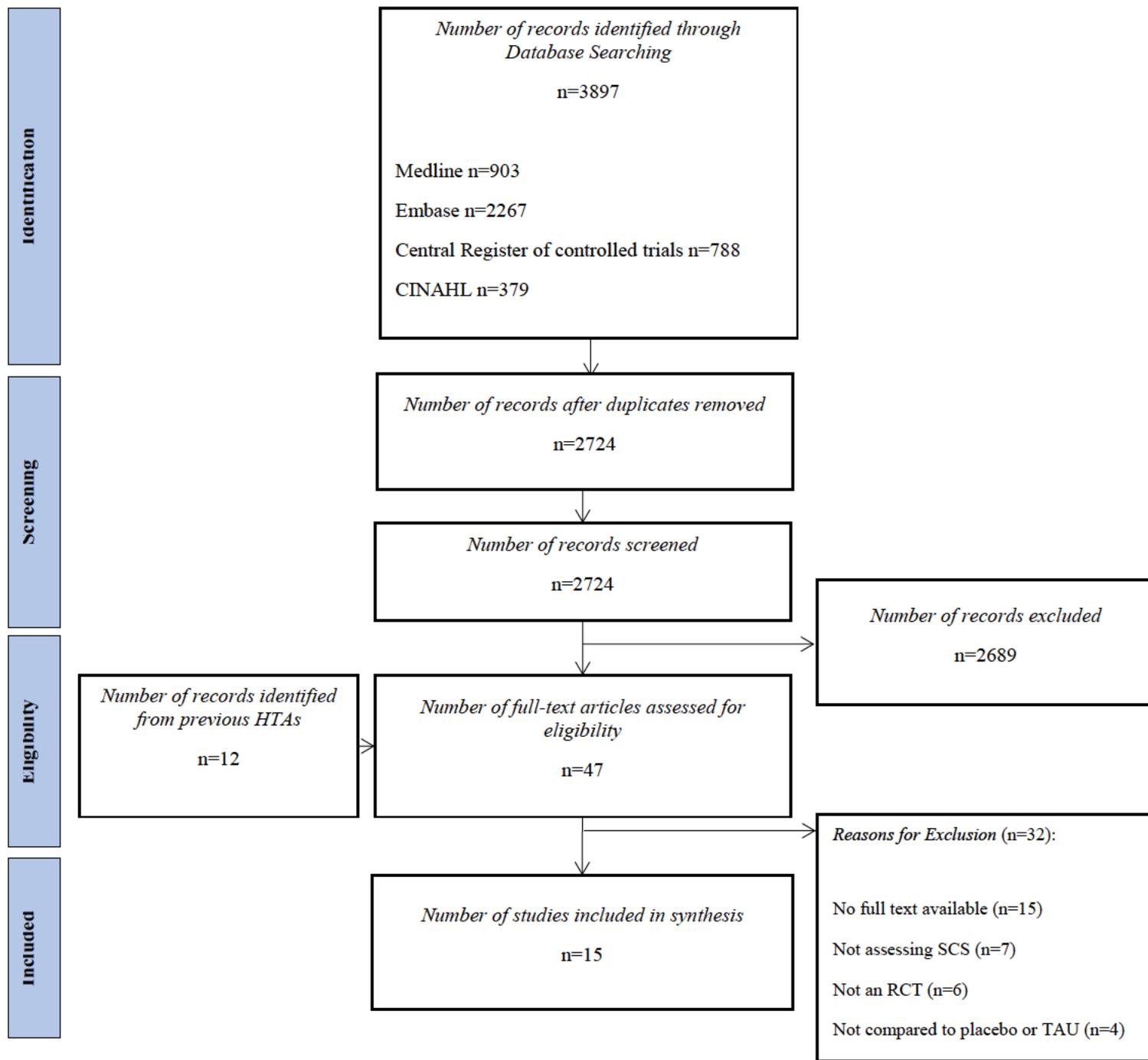
Data were too heterogeneous to meta-analyze. The results are reported narratively below.

10.3 Results

After database and hand-searching, 2,724 potentially relevant abstracts were included and 35 full texts were reviewed for eligibility (Figure 9). Twelve studies were identified within the previous HTA and assessed for inclusion. Fifteen RCTs were included in the final analysis. Six were from the Netherlands, two from the UK, and one each from Belgium, Canada, Germany, Italy, Sweden, Switzerland, and the US.

Five RCTs included patients with failed back surgery syndrome, three each assessed refractory angina, and refractory diabetic neuropathy, two assessed critical limb ischemia, and one each assessed myelomalacia, complex regional pain syndrome, and chronic low back pain. One included patients with both FBSS and myelomalacia.⁹² Most (n=8) RCTs compared SCS to conventional medical management or best practices. Five compared different settings or frequencies to sham and two compared SCS to no SCS. Detailed study characteristics are provided in Appendix D.

Figure 9. Study Inclusion Flowchart SCS Non-Cancer Pain



10.3.1 Quality of Included Studies

Of the RCTs included, eight were low risk of bias, four were high risk of bias, and three were of unclear risk of bias. Full results are available in Appendix E. All RCTs had low or some concerns regarding bias due to randomization, deviation, and reported results. Four RCTs had high measurement bias, and two had high bias due to missing outcomes (Appendix E).

10.3.2 Outcomes Related to Pain

Thirteen of the included studies reported outcomes related to pain scores. The most commonly used measure was the VAS (n=11). Of these, seven reported significant changes, three reported no significant improvement, and one did not indicate significance (Table 13). Three RCTs utilized the McGill Pain Questionnaire. Two of these^{93,94} reported statistically significant improvements ($p<.001$ and $p<.05$, respectively), and one⁹⁵ reported no significant improvement (no p-value provided). Two RCTs utilized the Numeric Pain Rating Scale, both of which identified statistically significant improvements ($p<.05$ and $p<.001$, respectively).^{94,96} Finally, the Pain Vigilance and awareness Questionnaire was utilized in one study which reported a statistically significant improvement ($p<.05$).⁹²

10.3.3 Other Outcomes

One RCT utilized the Patients' Global Impression of Change scale to assess patients' response to treatment.⁸⁵ More patients responded to high-frequency SCS (42.4%) than patients with sham (30.3%); no p-value was provided. The Global Perceived Effect scale was utilized in one RCT; patients receiving SCS reported statistically significant improvements in satisfaction ($p<.001$) and improvements overall ($p=.004$).⁹³

Quality of life was assessed in four RCTs.^{42,85,97,98} Two different measurements were used: the MPQ quality of life scale⁴² and the EQ-5D index.^{85,97} One measured health-related quality of life by assessing daily activity and social activity.⁹⁸ Three reported significant improvements in quality of life ($p<.001$ ^{42,97} and $p<.05$ ⁹⁸) and no significant improvement was reported in one ($p=.78$).

Opioid use was assessed in one RCT.⁹⁹ Patients utilizing SCS reported stable or decreased opioid use (87%) more frequently than patients only receiving conventional medical management (58%, $p=.025$).

Limb salvage rates were reported in two RCTs assessing SCS for critical limb ischemia.^{95,100} Limb salvage rates were not significantly improved in any of the trials.

Finally, exercise capacity was assessed in two RCTs.^{98,101} Patients with refractory angina receiving SCS had a longer time to angina during exercise (319 seconds) than those without SCS (246 seconds, $p=.01^{101}$), and also had a significantly longer mean exercise duration (827 seconds vs. 694 seconds, $p<.03^{98}$).

10.4 Conclusions

Results regarding the ability of spinal cord stimulation to significantly improve pain-related outcomes in non-cancer pain are variable. Of the 13 RCTs utilizing any pain scale, nine reported significant improvements and three reported no significant improvements. Quality of life was significantly improved in three of four RCTs, as well as opioid use and exercise capacity.

Table 13. SCS Non-cancer Pain Trial Outcomes Summary

Study	Pain scores				Other outcome measures					
	Improvement in VAS score	Improvement in NRS score	Improvement in PVAQ score	Improvement in MPQ score	Improvement in PGIC score	Improvement in GPE score	Quality of life	Opioid use	Limb salvage rates	Exercise capacity
Al-Kaisy, SCS Frequency Study, 2017	✓	—	—	—	—	—	—	—	—	—
De Ridder, 2013	✓	—	✓	—	—	—	—	—	—	—
de Vos, 2014	✓	—	—	—	—	—	✓	—	—	—
deJongste, 1994	—	—	—	—	—	—	✓	—	—	✓
Duarte, 2015	✓	—	—	—	—	—	✓	—	—	—
Hautvast, 1998	X	—	—	—	—	—	—	—	—	✓
Jivegard, 1995	✓	—	—	—	—	—	—	—	X	—
Kriek, 2016	✓	—	—	✓	—	✓	—	—	—	—
Kumar, PROCESS Trial, 2007	✓	—	—	—	—	—	—	—	—	—
Lanza, the SCS-ITA Trial, 2011	No indication of significance	—	—	—	—	—	—	—	—	—
North, 2005	—	—	—	—	—	—	—	✓	—	—
Perruchoud, 2012	X	—	—	—	No indication of significance	—	X	—	—	—
Schu, 2013	—	✓	—	✓	—	—	—	—	—	—

Slangen, 2014	—	✓	—	—	—	—	—	—	—	—
Spincemaille, ESES trial, 2000	X	—	—	X	—	—	—	—	X	—

Shading indicates primary outcome; ✓ = significant change; X = no significant change; -- = not reported

GPE: Global Perceived Effect scale; MPQ: McGill Pain Questionnaire; NRS: Numeric Pain Rating Scale; PGIC: Patients' Global Impression of Change scale; PVAQ: Pain Vigilance and Awareness Questionnaire; VAS: Visual Analogue Scale

11 Systematic Review of the Clinical Effectiveness of PNS and PNfS for Non-cancer Pain

Summary:

- Nine of the articles reporting on 6 trials met eligibility criteria for PNS.
- Three trials assessing ONS for chronic migraines concluded that ONS is beneficial for treating headache pain due to chronic migraines.
- Two trials that assessed ONS for fibromyalgia reported that PNS appeared beneficial for treating fibromyalgia-related pain.
- One trial assessed sphenopalatine ganglion (SPG) stimulation for cluster headaches and determined that on-demand SPG stimulation is effective for chronic cluster headaches.
- One study was found that subcutaneous nerve field stimulation is effective for chronic pain due to failed back surgery syndrome.

11.1 Purpose

To assess clinical effectiveness of peripheral nerve stimulation (PNS) or peripheral nerve stimulation (PNfS) for non-cancer chronic pain.

11.2 Methods

11.2.1 Search Strategy

A systematic review was performed. A prior HTA by NICE published in 2012 regarding PNS and PNfS was identified as relevant during the systematic review of HTAs on neuromodulation and a search was performed to update the findings of the NICE HTA. MEDLINE, EMBASE, PsycINFO, the Cochrane Central Register of Controlled Trials and CINAHL were searched from inception to May 2018. The search strategy was developed by a medical librarian. The search strategy combined words associated with peripheral nerve stimulation or peripheral nerve field stimulation, such as “peripheral nerve stimulation” or “electric stimulation therapy,” with words associated with pain management and chronic non-cancer pain, such as “pain management,” “non-cancer pain” or “chronic pain.” Terms were searched as both text words (title/abstract) and subject headings (e.g. MeSH). Searches were limited to English or French, human studies, and randomized controlled trials. The full search strategy can be found in Appendix F.

11.2.2 Study Selection

RCTs examining PNS or PNfS for chronic non-cancer pain were included. All abstracts were reviewed in duplicate. Any abstract included by either reviewer proceeded to full-text review.

Studies were excluded if they were not RCTs, were not for chronic non-cancer pain, used other neuromodulation techniques, did not compare using a placebo setting, or were animal studies. Relevant systematic reviews were not included but searched for potentially relevant articles.

Studies included after abstract review were screened in duplicate. Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion in Table 14. Any discrepancy between reviewers was resolved through discussion and consensus.

Table 14. Inclusion and Exclusion Criteria PNS and PNfS Non-cancer Pain

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Patients implanted with PNS or PNfS for non-cancer pain • English or French language only • RCT study design • Adult population • Outcomes of interest: <ul style="list-style-type: none"> ○ Pain assessment (e.g. VAS, McGill Pain Questionnaire) ○ HR QoL ○ AE/SAE ○ Healthcare utilization (e.g. intake of oral pain medication) ○ Patient satisfaction 	<ul style="list-style-type: none"> • Not an RCT • Not chronic non-cancer pain • Other neuromodulation technologies • No placebo comparator setting • Animal studies • Does not report original data • Full-text not available

11.2.3 Data Extraction

Data were extracted by one reviewer using a standard data extraction form and verified by a second reviewer. Extracted data included study characteristics (author/date, trial if known, and country), the intervention used in the trial, patient characteristics, and primary outcome. The results were synthesized and reported narratively.

11.2.4 Quality Assessment

During data extraction, quality assessment was completed. Quality was assessed using the Cochrane Tool for Assessing Risk of Bias.⁹¹ Using the Cochrane Risk of Bias tool, each RCT is assessed for seven areas of bias (random assignment generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome

data; selective reporting; and any additional potential sources of bias). Each study was assigned “low,” “high,” or “unclear” risk of bias for each of these seven potential sources of bias.

11.3 Results

The updated search returned 2,397 titles and abstracts (see Figure 10) of which 47 proceeded to full-text review. A NICE HTA published in 2012 assessing PNS, PNfS and percutaneous electrical nerve stimulation (PENS) was identified as relevant during the systematic review of HTAs on neuromodulation. Twenty-two studies included in the NICE report were reassessed for inclusion in the updated review. Fifty-nine were excluded due to not reporting on the technology of interest (n=19), the technology not being implanted (10), not reporting on an outcome of interest (n=2), not including placebo comparators (n=2), not being relevant to chronic non-cancer pain (n=2), not reporting original data (n=5), being a duplicate (n=5), or the full-text not being available (n=14). Full-text review resulted in the inclusion of nine studies for PNS and one study for PNfS. A summary of study outcomes is presented in (Table 15).

11.3.1 Study Characteristics

For the nine included articles on PNS (Appendix G), six assessed occipital nerve stimulation for chronic migraines; however four of these publications were from the same trial conducted in the US.¹⁰²⁻¹⁰⁵ Thus, there are three trials in total that assessed occipital nerve stimulation for chronic migraines; two were conducted in the US^{102,106} and one was conducted in Germany.¹⁰⁷ Two studies assessed occipital nerve stimulation for fibromyalgia; these were conducted in Belgium.^{108,109} One study assessed sphenopalatine ganglion (SPG) stimulation for chronic cluster headaches and was conducted in Belgium.¹¹⁰

The included study for PNfS assessed subcutaneous nerve field stimulation for FBSS (see Appendix H). This study was conducted in the UK.¹¹¹

11.3.2 Quality of Included Studies

Of the studies included, eight were low risk of bias, two were unclear risk of bias, and none were high risk of bias. Full results are available in Appendix I. One RCT had some concerns regarding bias due to randomization. One RCT had some concerns regarding bias due to deviations from intended interventions, bias due to missing outcome data, and measurement bias (Appendix J).

11.3.3 PNS for Chronic Migraine

Three trials investigated the effectiveness of PNS of the occipital nerve for chronic migraines using a mix of measures including reduction in number of headache days, Visual Analogue Scale (VAS), and MIDAS scores.¹⁰²⁻¹⁰⁷ The most commonly used measures were number of headache days experienced per month and VAS scores. Two trials reported improvements in number of headache days experienced each month from baseline.^{102,103,106} One trial reported improvements in VAS scores,¹⁰⁷ while one trial found no significant improvement in patients achieving a 50% reduction in pain, however it did find a significant improvement in patients achieving at least 30% reduction in pain.^{103,104} All three trials concluded that the evidence supported the efficacy of ONS for headache pain associated with chronic migraines.

One trial assessed the relation between adverse events (AEs) and previous experience of device implanters.¹⁰⁵ It reported 221 AEs occurred in 111 out of 157 total enrolled patients in the 52 weeks following implantation. The study reported that AEs occurred more frequently when implanters were less experienced (had previously performed five or less device implants) and concluded that as implanters become more experienced, a significant reduction in device- and procedure-related AEs can be expected.

11.3.4 PNS for Fibromyalgia

Two trials assessed PNS of the occipital nerve for fibromyalgia.^{108,109} One reported significant reductions in VAS and PCS scores¹⁰⁸ while the other reported reduction in FIQ scores.¹⁰⁹ Both concluded that ONS is beneficial for pain related to fibromyalgia.

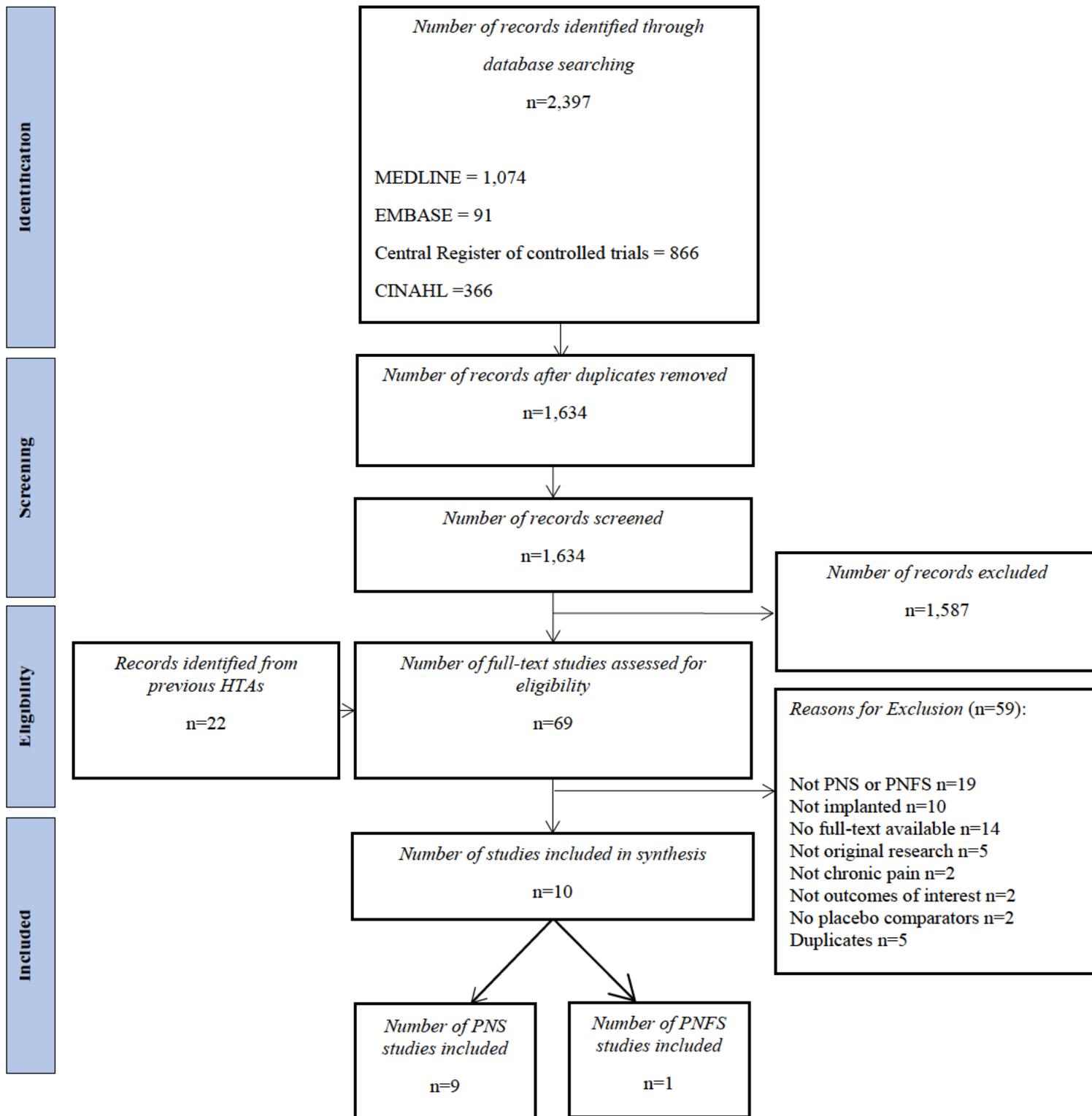
11.3.5 PNS for Chronic Cluster Headaches

One trial measured pain relief at 15 minutes stimulation to assess SPG for chronic cluster headaches.¹¹⁰ This trial found significantly more patients achieved pain relief through full-stimulation using SPG ($p < 0.0001$).

11.3.6 Clinical Effectiveness of PNfS

One study assessed effectiveness of subcutaneous nerve stimulation for FBSS.¹¹¹ This trial assessed the number of patients that achieved at least 50% reduction in pain nine months after baseline. It reported a significant reduction in pain for patients receiving the intervention plus optimized medical management (33.9% of patients) compared to control group patients receiving optimized medical management only (1.9%).

Figure 10. Study Inclusion Flowchart PNS and PNFS Non-cancer Pain



11.4 Conclusions

Three trials were identified that assessed PNS of the occipital nerve for chronic migraines. All three determined that PNS was effective for pain due to chronic migraines. Two trials were identified that assessed PNS of the occipital nerve for fibromyalgia-related pain; both trials concluded that PNS was effective for treating fibromyalgia-related pain. One trial determined that SPG was effective for chronic cluster headaches.

One trial assessing the effectiveness of PNFS for FBSS reported that subcutaneous nerve stimulation was effective in treating pain due to FBSS.

Table 15. PNS/PNfS Non-cancer Pain Trial Outcomes Summary

Study	Intervention, Condition	Pain scores						Other outcome measures	
		Improvement in VAS score	Reduction in number of headache days	Improvement in PCS	Pain Disability score (MIDAS)	Pain relief/pain freedom	MPQ	FIQ scores	AEs
Dodick, Mekhail, Sharan, Silberstein *	PNS of the occipital nerve, chronic migraine	X	✓	—	✓	—	—	—	✓
Slotty	PNS of the occipital nerve, chronic migraine	✓	—	—	—	—	✓	—	—
Saper	PNS of the occipital nerve, chronic migraine	—	✓	—	—	—	—	—	—
Plazier 2014	PNS of the occipital nerve, fibromyalgia	✓	—	✓	—	—	—	—	—
Plazier 2015	PNS of the occipital nerve, fibromyalgia	—	—	—	—	—	—	✓	—
Schoenen	SPG, cluster headaches	—	—	—	—	✓	—	—	—

Shading indicates primary outcome; ✓ = significant change; — = not reported

VAS: Visual Analogue Scale; PCS: Pain Catastrophizing Scale; MIDAS: Migraine Disability questionnaire; MPQ: McGill Pain Questionnaire; FIQ: Fibromyalgia Impact Questionnaire; AEs: Adverse Events

* All from same clinical trial (Clinical trial Identifier: NCT00615342 on clinicaltrials.gov website)

12 Systematic Review of the Clinical Effectiveness of TENS of the Supraorbital Nerve for Non-cancer Pain

Summary:

- There were 520 records retrieved in the search and three additional publications retrieved from a previous NICE report of which 12 proceeded to full-text review.
- One record met eligibility criteria and proceeded to data extraction
- Clinical effectiveness and safety evidence is limited and of non-RCT quality

12.1 Purpose

To synthesize studies on the clinical effectiveness and safety of TENS of the supraorbital nerve for non-cancer pain.

12.2 Methods

12.2.1 Search Strategy

A systematic review was conducted. A NICE interventional procedure guidance (IPG) was published in 2016 regarding TENS of the supraorbital nerve for treating and preventing migraines. It was identified as relevant during the systematic review of HTAs on neuromodulation and a search was performed to update the findings. The NICE IPG searched MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases from inception to July 2015. Trial registries and the internet were also searched. To supplement that work, MEDLINE, EMBASE, PsycINFO, the Cochrane Central Register of Controlled Trials and CINAHL were searched from January 2015 to May 2018. The search strategy was developed by a medical librarian. The search strategy combined words associated with TENS of the supraorbital nerve such as “supraorbital nerve stimulation” or “supraorbital neurostimulation,” with words associated with pain management and non-cancer pain, such as “pain management,” “non-cancer pain,” or “intractable pain.” Terms were searched as both text words (title/abstract) and subject headings (e.g. MeSH). Searches were limited to English or French, human studies, and randomized controlled trials. The full search strategy can be found in Appendix K.

12.2.2 Study Selection

All studies examining TENS of the supraorbital nerve for non-cancer pain were included. All abstracts were reviewed in duplicate. Any abstract included by either reviewer proceeded to full-text review. Studies were excluded if they did not meet the inclusion criteria, were single case

studies, did not report original data, used other neuromodulation techniques, or were animal studies. Identifying chronic non-cancer pain for inclusion was aided through application of the ICD-11 chronic pain classifications.⁸

Studies included after abstract review were screened in duplicate. Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion in Table 16. Any discrepancy between reviewers was resolved through discussion and consensus.

Table 16. Inclusion and Exclusion Criteria TENS of the Supraorbital Nerve

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Patients undergoing TENS supraorbital nerve stimulation for non-cancer pain • Chronic pain • English or French language only • All study designs (except single case studies) • Adult population • Outcomes of interest: <ul style="list-style-type: none"> ○ Pain assessment (e.g. VAS, McGill Pain Questionnaire) ○ HR QoL ○ AE/SAE ○ Healthcare utilization (e.g. intake of oral pain medication) ○ Patient satisfaction 	<ul style="list-style-type: none"> • Other neuromodulation technologies • Animal studies • Does not report original data • Full text not available • Single case study design

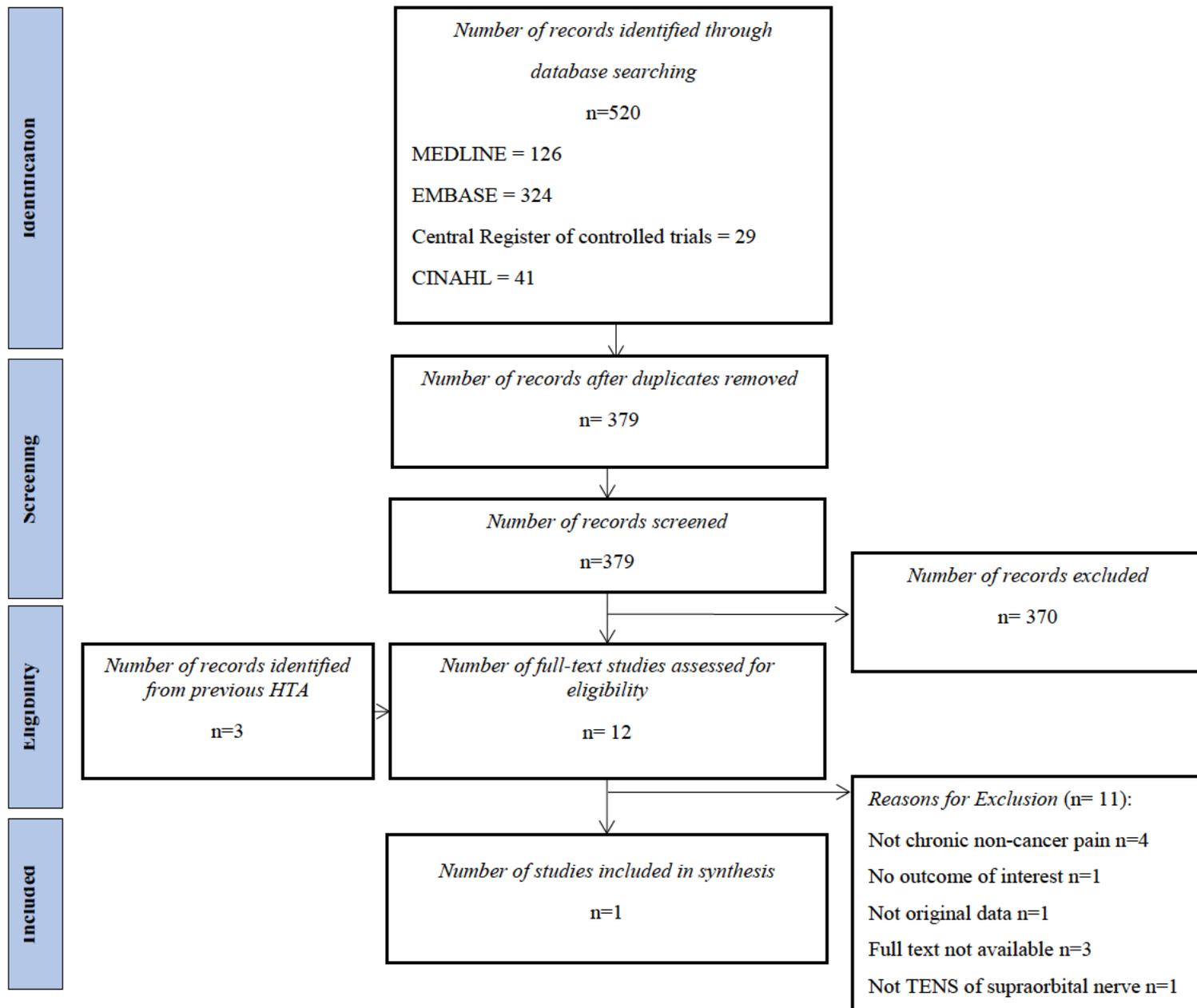
12.2.3 Data Extraction

Extracted data included: characteristics (author/date, country, study design, study objectives, outcomes reported). Discrepancies between reviewers during data extraction were resolved through consensus.

12.3 Results

The searched returned 379 titles and abstracts (Figure 11). Of the abstracts reviewed, nine proceeded to full text review. Eight were excluded due to not reporting an outcome of interest (n=1), not being relevant to chronic non-cancer pain (n=4) or TENS of the supraorbital nerve (n=1), not reporting original data (n=1), or the full text not being available (n=3). Full text review resulted in the inclusion of one study.

Figure 11. Study Inclusion Flowchart Supraorbital TENS Non-cancer Pain



12.3.1 Study Characteristics

The included study was conducted in Italy and published in 2017. It was a prospective, open-label preliminary trial with 23 patients enrolled. The patients selected were adults suffering from chronic migraine for at least one year, had no record of participation in medication overuse withdrawal programs over the previous year, had normal neurological and neuroimaging findings, and were not pregnant. Of the 23 patients enrolled, 18 (78.3%) were female and 14 (60.9%) had medication overuse. The mean age of participants was 43.7 ± 13.6 years. Mean duration of headache condition was 26.4 ± 12.8 years and mean duration of the chronic phase was 10.7 ± 8.7 years.

The patients received active treatment with the Cefaly device's Programme 2. The device includes a self-adhesive bipolar electrode to affix to the forehead for stimulation of the supraorbital nerves. It generates biphasic rectangular impulses for a fixed period of 20 minutes. All participants received training and instructions to use the device for 20 minutes each day over the four month study period. Monthly appointments were conducted to follow the patient experience. Primary endpoints for the study were at least 50% reduction in headache days per month, and at least 50% reduction in headache relief medication consumption.

12.3.2 Clinical Effectiveness and Safety

Four patients (17.4%) dropped out within the first month of the study due to a new comorbidity (n=1) or inability to tolerate the stimulation (n=3). The side effects that prompted patient drop out in three patients were neck tension and worsening of headache. All other participants completed the four month follow-up (n=19). Data analysis was completed on the 19 (82.6%) patients that completed the study. The mean decrease in migraine days per month was 31.0% and mean decrease in medication consumption was 49.6%. Twelve patients (52.2%) met the medication reduction endpoint with a mean reduction of 65.5%. Eight participants (34.8%) achieved both endpoints, for this group mean reduction in headaches per month was 57.9% and mean reduction in medication consumption was 68.8%. The improvements were achieved gradually over the four month study period. The 11 participants (47.8%) that did not achieve both endpoints had an average reduction in headaches per month of 15.3% and a reduction in medication consumption of 35.9%.

12.3.3 Limitations

There are some notable limitations of the included study. The study was non-controlled and preliminary in nature with relatively few patients enrolled and an intention to treat analysis was not conducted. However, the purpose of the study was to investigate justification for more rigorous investigations.

12.4 Conclusions

The evidence for clinical effectiveness and safety of TENS of the supraorbital nerve in non-cancer chronic pain is limited and of non-RCT quality.

13 Systematic Review of the Clinical Effectiveness of Intrathecal Pumps for Cancer and Non-cancer Pain

Summary

- There were 700 records retrieved in the search, of which eight were included in the final analysis.
- Risk of bias was variable across the studies, with four being low risk of bias, three being uncertain risk, and one high risk of bias.
- Seven RCTs assessed pain using multiple pain scores. Four of these reported a significant improvement in pain, and three reported no significant improvement.
- Other measured outcomes included quality of life, drug toxicity, changes in drug use, and adverse events. Only drug toxicity was consistently significantly improved.

13.1 Purpose

The purpose of this systematic review was to assess the safety and effectiveness of intrathecal pump for cancer and non-cancer pain.

13.2 Methods

13.2.1 Search Strategy

A systematic review was conducted. MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials were searched from inception to May 2018. The search strategy was developed in consultation with a medical librarian. The search strategy combined words associated with intrathecal pumps, such as “infusion pumps” or “intrathecal drug administration,” with words associated with pain management, such as “pain management,” and specific types of pain, such as “chronic pain.” The Cochrane RCT filter was also applied to improve precision. Terms were searched as both text words (title/abstract) and subject headings (e.g. MeSH). Searches were limited to human studies. The search strategy is included in Appendix L. PRISMA guidelines were followed throughout the review.⁹⁰

13.2.2 Study Selection

To be included, studies had to assess the use of intrathecal pumps compared to a placebo for pain management. Studies were excluded if they were not a RCT, did not report on intrathecal pumps, were not in chronic pain patients and were did not published in English or French. Relevant systematic reviews and meta-analyses were not included, but were flagged and reference lists were searched for other potentially relevant articles. All abstracts were reviewed in duplicate.

Any abstract included by either reviewer proceeded to full text review. This initial screen was intentionally broad to ensure all relevant literature was captured.

Studies included after abstract review proceeded to full-text review. Full text review was completed in duplicate. Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion presented in Table 17. Any discrepancy between reviewers was resolved through discussion and consensus. If required, a third reviewer was consulted.

Table 17. Inclusion and Exclusion Criteria Intrathecal Pumps Cancer and Non-Cancer Pain

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> ● Pertaining to clinical effectiveness of intrathecal pumps for cancer and non-cancer pain ● English or French language only ● RCT study design ● Adult population ● Outcomes of interest: <ul style="list-style-type: none"> ○ Pain assessment (e.g. VAS, McGill Pain Questionnaire) ○ HR QoL ○ AE/SAE ○ Healthcare utilization (e.g. intake of oral pain medication) ○ Patient satisfaction 	<ul style="list-style-type: none"> ● Other pain-management techniques ● Not chronic pain ● Not an RCT ● Animal studies ● Does not report original data ● Full text not available ● Not English or French

13.2.3 Data Extraction

Data from the final included studies were extracted by one reviewer using a standard data extraction form, and data were verified by another reviewer. Details of the technology used, information on the intervention, patient characteristics, and primary and secondary outcomes were extracted.

13.2.4 Quality Assessment

During data extraction, quality assessment was completed. Quality was assessed using the Cochrane Tool for Assessing Risk of Bias.⁹¹ Using the Cochrane Risk of Bias tool, each RCT is assessed for seven areas of bias (random assignment generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome

data; selective reporting; and any additional potential sources of bias). Each study was assigned “low,” “high,” or “unclear” risk of bias for each of these seven potential sources of bias.

13.2.5 Data Analysis

Data extracted were too heterogeneous to allow for meta-analysis. Thus the results are summarized narratively below.

13.3 Results

After database and hand-searching, 700 potentially relevant abstracts were included and 23 full texts were reviewed for eligibility (Figure 12). Eight RCTs were included in the final analysis. All included studies were from the United States. Four assessed non-cancer pain, three assessed cancer-associated pain, and one assessed cancer- or HIV-associated pain. Three compared varying doses to a saline placebo.¹¹²⁻¹¹⁴ Detailed study characteristics are provided in Appendix M.

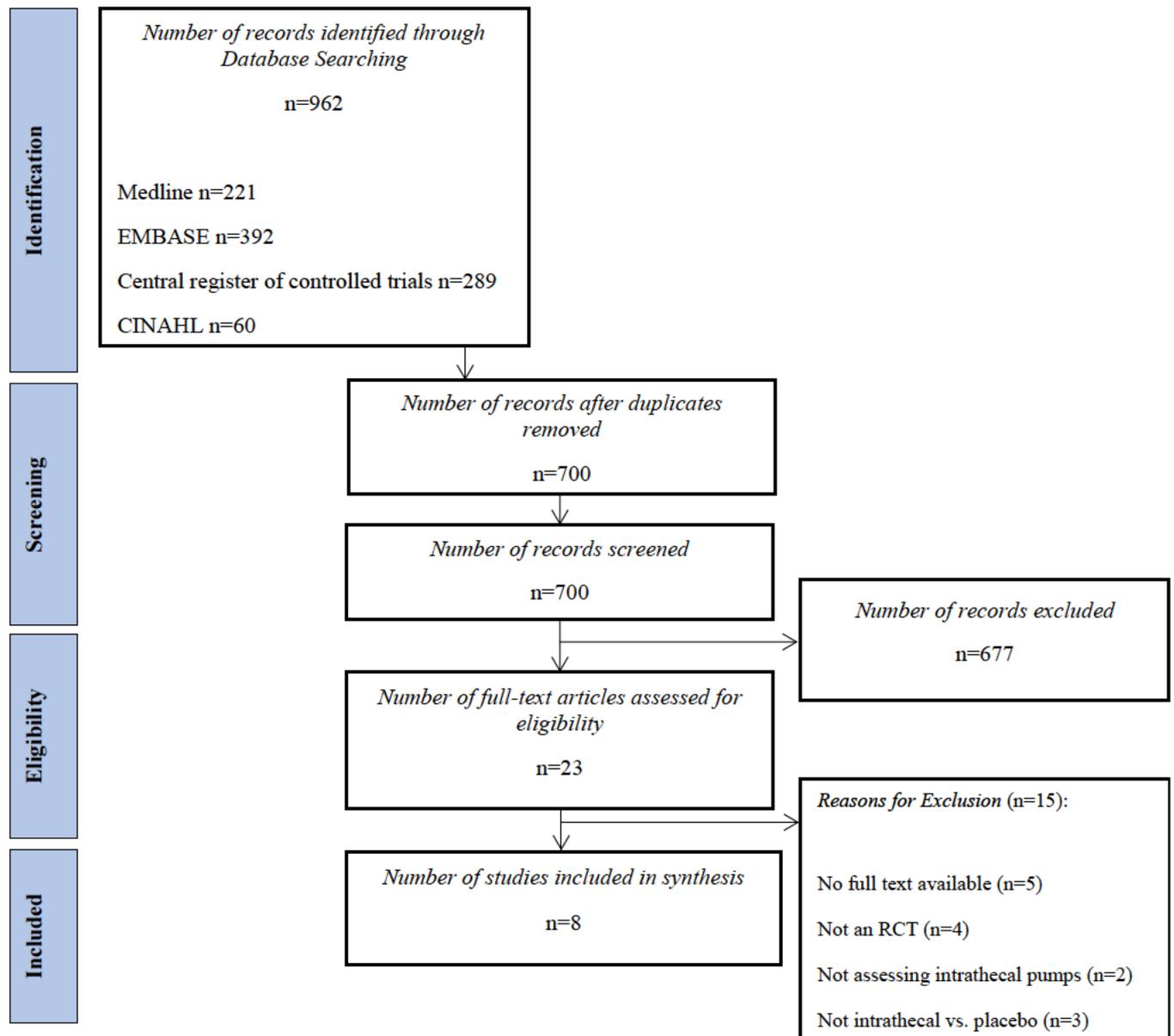
13.3.1 Quality of Included Studies

Four RCTs had low risk of bias, three had some concerns regarding bias, and one was high risk of bias (Appendix N). All studies had low risk of bias for randomization and missing outcome data, and all but one had low bias for reported results. One study had high risk of bias for both bias from deviation and bias from measurement.¹¹⁵ Another had uncertain risk of bias for bias from deviation and bias from measurement.¹¹⁶ One had uncertain risk of bias from measurement.¹¹⁷ Finally, one had uncertain bias from reported results.¹¹²

13.3.2 Outcomes Related to Pain

Seven RCTs assessed pain using multiple pain scores (Table 18). The most commonly used assessment measure was the VAS. Of those utilizing this measurement, four^{115,116,118,119} reported improved outcomes and two reported no significantly improved outcomes.^{113,117} The Brief Pain Inventory (BPI) was utilized in two RCTs, both of which did not report a significant improvement.^{113,114} The Numeric Pain Rating Scale (NPRS) was utilized in one study and was not significantly improved.¹¹⁴ Finally, the McGill Pain Questionnaire was utilized in one RCT and was significantly improved in those with intrathecal pumps.¹¹⁹

Figure 12. Study Inclusion Flowchart Intrathecal Pumps Cancer and Non-cancer Pain



13.3.3 Adverse Events

Adverse events were reported in three RCTs (Table 18).^{112,118,119} One reported no significant differences in adverse events for those receiving octreotide intrathecally (no p-value given).¹¹² One RCT reported a significant difference in any adverse event experienced ($p=.001$) for those receiving ziconotide intrathecally (94.7%) compared to placebo (72.1%).¹¹⁹ One reported increased adverse events in those receiving ziconotide intrathecally (30.6%) compared to saline placebo (10.0%), but no measure of significance was provided.¹¹⁸

13.3.4 Other Outcomes Assessed

13.3.4.1 Drug Toxicity

Drug toxicity was assessed in three RCTs.¹¹⁵⁻¹¹⁷ All three reported significantly improved drug toxicity ($p<.0001$, $p=.002$, and $p=.004$, respectively). This change was not significant at 12-week follow-up in one RCT ($p=.23$ ¹¹⁶).

13.3.4.2 Quality of Life

Quality of life was assessed in one RCT utilizing the SF-36 instrument.¹¹⁴ There were no significant differences between those with intrathecal pumps and those without ($p=.392$).

13.3.4.3 Change in Drug Use

Changes in drug use were assessed in one RCT.¹¹⁴ There was no significant difference in opioid use in those receiving gabapentin intrathecally ($p=.139$).

13.4 Conclusions

Drug toxicity was improved in all three RCTs in which it was assessed. All other outcomes, however, had varying outcomes or were only assessed in one RCT. Overall, results regarding pain reduction were variable with four RCTs reporting significant improvements and three RCTs reporting no significant improvement on at least one pain scale. Further, significant increases in adverse events were reported in two RCTs. Thus the ability of intrathecal pumps to significantly improve pain without increased adverse events is low.

Table 18. Intrathecal Pump Cancer and Non-cancer Trial Outcomes Summary

Study	Pain scores				Other outcome measurements			
	Improvement in VAS score	Improvement in BPI score	Improvement in NPRS score	Improvement in MPQ score	Improvement in QoL	Improvement in drug toxicity	Change in drug use	Any adverse event
Deer, US, 2005	—	—	—	—	—	—	—	X
Deer, US, 2006	X	X	—	—	—	—	—	—
Rauck, US, 2013	—	X	X	—	X	—	X	—
Smith & Coyne, The Cancer Pain Trial, US, 2005	✓	—	—	—	—	✓	—	—
Smith, US, 2005	✓	—	—	—	—	✓	—	—
Smith, for the Implantable Drug Delivery Systems Study Group, US, 2002	X	—	—	—	—	✓	—	—
Staats, US, 2004	✓	—	—	—	—	—	—	No indication of significance given
Wallace, Elan Pharmaceuticals Inc., US, 2006	✓	—	—	✓	—	—	—	✓

Shading indicates primary outcome; ✓ = significant change; X = no significant change; — = not reported
 BPI: brief pain inventory; MPQ: McGill Pain Questionnaire; NPRS: numeric pain rating scale; QoL: quality of life; VAS: visual analogue score

14 Ongoing Clinical Trials

Summary

- Fourteen relevant ongoing clinical trials were identified on clinicaltrials.gov.
- Ten relevant completed clinical trials were identified, six of which have not reported their results to date.

14.1 Overview of completed trials

Ten completed trials were identified (Table 19). Four of these trials assessed spinal cord stimulation, one included spinal cord stimulation and intrathecal pumps, and five assessed peripheral nerve stimulation. Six of the ten trials did not include reports of the study results. Of the completed clinical trials, five were randomized control trials.

14.2 Overview of active trials

Fourteen trials were identified that are currently underway, actively recruiting participants, or planning to recruit participants (Table 20). There were two active trials identified, seven currently recruiting participants, three not yet recruiting participants, and two with unknown status. The neuromodulation treatments being assessed in these trials were spinal cord stimulation (N=10) and peripheral nerve stimulation (N=4). Six of the clinical trials were randomized control trials.

Table 19. Completed Clinical Trials registered on clinicaltrials.gov

Study	Intervention Type	Design	Condition/ Population of interest	Primary outcome of interest	Completion date
SUNBURST (Success Using Neuromodulation With BURST) Study (NCT02011893)	SCS	RCT, n=173	Chronic intractable pain of the trunk and/or limbs; aged 22 years or older.	Visual Analog Scale (VAS) Pain Diary Scores for Average Overall Pain	January 2017
Evaluate St Jude Medical Prodigy Neuromodulation for FBSS or Chronic Pain of the Trunk and/or Limbs https://clinicaltrials.gov/ct2/show/NCT02143791	SCS	Case Control, n=126	Adult aged 18 years or older, with chronic, intractable pain of the trunk and/or limbs.	Percentage of pain relief at the 3-month visit compared to baseline visit, as measured by the VAS.	October 2016
A Prospective Clinical Outcomes Registry https://clinicaltrials.gov/ct2/show/NCT01305525	SCS	Prospective trial (non-randomized), n=614	Adults 18 years and older; implanted with a St. Jude Medical Neuromodulation system	Patient reported outcomes over time (2 yrs)	April 2014
Efficacy Study of the Octapolar Lead in Patients With Failed Back Surgery Syndrome (FBSS) With Chronic Pain https://clinicaltrials.gov/ct2/show/NCT01096147	SCS	Non-randomized open label trial, n=80	Failed Back Surgery Syndrome.	Pain suppression in low back and/or leg (VAS)	Nov 2013
Implantable Systems Performance Registry https://clinicaltrials.gov/ct2/show/NCT00959296	Includes SCS and Pumps	Prospective trial (non-randomized), n=10,981	Patients scheduled for implant/ replacement with a market-released Medtronic implantable drug pump, spinal cord stimulator, and other products	Product performance	Sep 2016.
Electrical Stimulation for the Treatment of Post-Stroke Shoulder Pain https://clinicaltrials.gov/ct2/show/NCT01094301	PNS	Prospective Pilot Study (non-randomized), n=28	Post-stroke shoulder pain, aged 21 years or older	Change in pain intensity	July 2017
Optimal Stimulation Programming for Spinal Peripheral Neuromodulation https://clinicaltrials.gov/ct2/show/NCT02346383	PNS	RCT, n=42	22 Years to 90 Years, patients with chronic pain	Pain, measured by numeric rating scale	June 2016
Bioness StimRouter Neuromodulation System for Chronic Pain Therapy https://ClinicalTrials.gov/show/NCT01592344	PNS	RCT, n=94	Adults 22 years or older; severe intractable chronic pain of peripheral nerve origin associated with post	Number of participants with a pain reduction greater than or equal to 30%, using Brief Pain Inventory (BPI),	July 2015

			traumatic/post surgical neuralgia for ≥ 3 months.	compared with baseline.	
Electrical Stimulation for the Treatment of Chronic Post-Stroke Shoulder Pain Using the Smartpatch System https://clinicaltrials.gov/ct2/show/NCT01847885	PNS	RCT, n=88	Post-stroke shoulder pain; at least 6 months after stroke that caused shoulder pain.	Change From Baseline Shoulder Pain Intensity at End of Treatment (daily diary using BPI).	Nov 2016.
Occipital Nerve (C2) Stimulation in the Treatment of Fibromyalgia https://clinicaltrials.gov/ct2/show/NCT01298609	Occipital Nerve Stimulation (PNS)	RCT, n=40	Fibromyalgia with chronic pain for ≥ 3 months; aged 18 years or older	Change in Fibromyalgia Impact Questionnaire (FIQ) score at end of treatment (from baseline)	Jan 2013

Table 20. Active Clinical Trials registered with clinicaltrials.gov

Study	Status	Intervention Type	Design	Condition/ Population of interest	Primary outcome of interest	Expected completion date
Wireless High Frequency Spinal Cord Stimulation for Chronic Pain https://clinicaltrials.gov/ct2/show/NCT02514590	Active	SCS	RCT N=80	Chronic back or back and leg pain refractory to standard medical treatment for Failed Back Surgery Syndrome (FBSS); 18 years and older.	Pain score (50% reduction in Visual Analog Score compared to baseline)	Nov 2018
Effectiveness of the Precision Spinal Cord Stimulator System at Sub-Perception Amplitude https://clinicaltrials.gov/ct2/show/NCT02314000	Active	SCS	RCT N=146	Chronic pain of the trunk and/or limbs; adults 22 years and older.	Pain score ($\geq 50\%$ reduction in overall pain intensity from baseline)	Dec 2018
Clinical Outcomes of the Freedom Spinal Cord Stimulation (SCS) System for the Management of Chronic Back and Leg Pain https://ClinicalTrials.gov/show/NCT02403518	Currently recruiting participants	SCS	Non-randomized, N=45	Chronic low back pain or pain in leg; aged 18 years and older	Percentage of pain relief experienced in pain area identified at baseline compared to 12 months post full implant (VAS)	April 2020
Opioid Reduction Following Spinal Cord Stimulation (REDUCE) https://clinicaltrials.gov/ct2/show/NCT02727985	Currently recruiting participants	SCS	RCT, N=120	Chronic pain; aged 18 years and older	Change in number of opioids from baseline to post-intervention at 6-months follow-up (pain scores and QoL secondary outcomes)	Dec 2019
NAVITAS: A Study to Characterize the Relationship Between Select Objective Metrics and Clinical Outcomes in Chronic Pain Patients Treated With Boston Scientific Neurostimulation Systems https://clinicaltrials.gov/ct2/show/NCT03240588	Currently recruiting participants	SCS	Non-randomized open label, N=960	Chronic pain; 18 years and older	Mean difference in pain intensity between baseline and 6 months post-neurostimulation trial visit	Dec 2023
Pilot Study to Examine the Feasibility of the	Currently	SCS	Non-	Chronic	Back pain reduction	Aug 2019

Dynamic Interferential Spinal Cord Stimulation System™ (DISCSS™) https://clinicaltrials.gov/ct2/show/NCT03341000	recruiting participants		randomized, N=10	neuropathic pain of trunk and limbs; age greater than 21 years and less than 80 years	as compared to baseline, using numerical rating scale (NRS)	
Quality of Life Outcomes in Spinal Cord Stimulation https://clinicaltrials.gov/ct2/show/NCT03249922	Currently recruiting participants	SCS	Non-randomized cohort study, N=76	Neuropathic pain, low back pain; patients aged 18 years to 90 years; failed conservative management	number of patients with ≥50% improvement in VAS Pain Score	Oct 2019
Electrical Stimulation for the Treatment of Back Pain Using Peripheral Nerve Stimulation (PNS) https://ClinicalTrials.gov/show/NCT03179202	Currently recruiting participants	Peripheral Nerve Stimulation (PNS)	Non-randomized open label, N=50	Back pain, lower back pain; aged 21 years or older	Change in "average pain" intensity (measured using Brief Pain Inventory), compared to baseline	July 2019
Postoperative Percutaneous Peripheral Nerve Stimulation on Acute and Chronic Amputation Pain https://clinicaltrials.gov/ct2/show/NCT03484429	Currently recruiting participants	PNS	RCT, N=16	Phantom limb pain, post-operative pain, neuroma, acute pain, chronic pain, residual limbs, amputation; aged 18 – 79 years.	Change from baseline in residual limb pain, using brief pain inventory questionnaire	March 2019
Intradural Percutaneous Stimulation https://clinicaltrials.gov/ct2/show/NCT03380104	Not yet recruiting	SCS	Non-randomized (open label), n=10	Chronic pain; aged 18 years to 85 years.	Establishment of paresthesia threshold, motor threshold, acute adverse pain responses (McGill Pain Questionnaire and Brief Pain Inventory (BPI).	June 2019
Sham-Controlled RCT on 10kHz High-Frequency Spinal Cord Stimulation for Chronic Neuropathic Low Back Pain (Modulate-LBP) https://clinicaltrials.gov/ct2/show/NCT03470766	Not yet recruiting	SCS	RCT, N=96	Chronic low back pain, onset over 12 months ago, neuropathic pain (adults over age of 18)	Changes in mean VAS back pain between intervention and control at 6 months post-randomization	August 2020

StimRouter™ for Pain Management in Post-stroke Shoulder Pain https://clinicaltrials.gov/ct2/show/NCT03093935	Not yet recruiting	PNS	Non-randomized, N=50	Adults age 18 or over with severe intractable chronic shoulder pain subsequent to stroke	Reduction of average pain at rest measured by numeric scale (BPI)	Sep 2019
The Pain Suppressive Effect of Alternative Spinal Cord Stimulation Frequencies https://clinicaltrials.gov/ct2/show/NCT02112474	Unknown status	SCS	RCT, N=30	Failed back surgery syndrome, neuropathic pain;	Pain suppression due to SCS (measured using VAS)	Unclear (due to be completed Nov 2016)
French Database of Occipital Nerves Stimulation in the Treatment of Refractory Chronic Headache Disorders https://clinicaltrials.gov/ct2/show/NCT01842763	Unknown status	Occipital nerves stimulation (PNS)	Non-randomized, N=50	Refractory Chronic Headache Disorders	“observation of a disease or medical condition under normal conditions”	Unclear (due to be completed Dec 2016)

15 Environmental Scan of Canadian Context

Summary

- Practitioners across Canada were contacted and eight responses were received for Calgary, Edmonton, Saskatoon, London, Toronto, Montreal, Quebec City, and Halifax.
- SCS and PNS are currently offered for non-cancer pain in all locations that responded. PNFS is offered in four locations, while tSNS and intrathecal pump are offered in three of the responding locations across Canada for non-cancer pain.
- SCS is used substantially more (over 200 cases annually) than other neuromodulation treatments (approximately 100 cases annually combined) for non-cancer pain.
- The only location that responded offering all five neuromodulation types for cancer pain is Toronto.

15.1 Purpose

To understand how neuromodulation is currently being used for patients with chronic cancer and non-cancer pain across Canada.

15.2 Methods

Practitioners in Canada were identified from websites of major neuromodulation societies, including the International Neuromodulation Society (INS) and the Canadian Neuromodulation Society (CNS). Additional names and contact details of practicing clinicians were also provided through a snowballing approach and through clinician interviews (see Section 18).

Individuals were contacted by email and asked to provide details regarding: which, if any, of five neuromodulation treatments types under review in this assessment are offered to patients at their practice; whether these are used for patients with cancer pain or non-cancer pain; and the approximate number of patients treated with these pain management therapies annually. The five neuromodulation therapies included: SCS; tSNS; PNS; PNfS; and intrathecal pump. Practitioners were also asked to provide further information on which protocols or guidelines were used for patient selection for these treatments. One patient care pathway was shared. Data was tabulated and narratively summarized.

15.3 Results

Thirteen individuals were contacted and eight responses were received. Data were provided for Calgary, Edmonton, Saskatoon, London, Toronto, Montreal, Quebec City, and Halifax.

Information was requested for other sites understood to be offering neuromodulation including Ottawa, Regina and Winnipeg, however no response was received. The data provided are synthesized in Table 21.

All of the five neuromodulation therapy types reviewed in this assessment are currently offered in Canada. The five neuromodulation types are being used for patients with non-cancer pain across multiple sites. One site (Toronto, ON) provides all five neuromodulation types for patients with cancer or non-cancer pain, however the respondent noted that there is no provincial funding for intrathecal pump in Ontario. Only one other site, Saskatoon, confirmed that they have provided neuromodulation (intrathecal pump) for patients with cancer pain, however none were provided in the past year. One site (Montreal) only provided details of neuromodulation types currently being offered and declined to specify which types of patients they are used for (cancer or non-cancer pain); they noted that any neuromodulation treatment is determined based on individual patient needs as part of multidisciplinary pain care management.

SCS and PNS are offered at all eight locations that responded. PNFS is offered at four locations, intrathecal pump is offered at four locations, and tSNS is offered at three locations. Substantially more patients are treated with SCS (approx. 200 annually on average) than other therapies.

15.3.1 Provision, by province

In Alberta and Nova Scotia, only SCS and PNS are performed (for non-cancer pain).

Saskatchewan offers all five neuromodulation types for non-cancer pain). All five are also offered in Quebec for patients with non-cancer pain, however it is unclear whether these are also available for patients with cancer pain. In Ontario, all five neuromodulation types are available for patients with cancer pain and patients with non-cancer pain.

Table 21. Neuromodulation treatment types currently offered across Canada, which patient types they are used for, and approximate numbers of patients treated annually.

Site/ Location	Neuromodulation Technology									
	Spinal Cord Stimulation (SCS) Estimated annual cases (n)		Transcutaneous supraorbital nerve stimulation (tSNS) Estimated annual cases (n)		Peripheral nerve stimulation (PNS) Estimated annual cases (n)		Peripheral nerve field stimulation (PNFS) Estimated annual cases (n)		Intrathecal Pump Estimated annual cases (n)	
	Non-cancer pain	Cancer pain	Non-cancer pain	Cancer pain	Non-cancer pain	Cancer pain	Non-cancer pain	Cancer pain	Non-cancer pain	Cancer pain
Calgary, AB	6-12	-	-	-	2	-	-	-	-	-
Edmonton, AB	8 (range 6-12)	-	-	-	2	-	-	-	-	-
Saskatoon, SK	34	-	3	-	4	-	3	-	-	0 this year (some done in the past)
London, ON	27	-	-	-	15	-	5	-	-	-
Toronto	50	2	10	1	10	1	5	1	Offered (but no funding in Ontario)	Offered (but no funding in Ontario)
Montreal*	Yes		No		Yes		No		Yes	
Quebec City	50-60	-	1-2	-	10	-	20	-	10	-
Halifax, NS	20	-	-	-	4	-	-	-	-	-

* Contact from Montreal (Montreal Neurological Hospital and Institute) was unable to provide a breakdown of numbers, but noted that any neuromodulation treatment is determined based on individual patient needs as part of multidisciplinary pain care management.

15.4 Conclusion

Data was provided for eight different sites across Canada for this environmental scan. The responses garnered through this scan indicated that all five of the neuromodulation types assessed in this HTA are currently used for patients with non-cancer pain across multiple sites in Canada. Considerably fewer neuromodulation types are used for patients with cancer pain. Only one site (Toronto, ON) provides all five neuromodulation types for patients with cancer or non-cancer pain. SCS and PNS are the only two neuromodulation types that are offered in all locations that responded. Of the five neuromodulation types, SCS is used substantially more than the other therapy types.

16 Current Context in British Columbia

Summary

- There are currently four BC hospital-affiliated pain programs providing some neuromodulation for pain: one in Vancouver Coastal (St. Paul's Hospital), two on Vancouver Island (Royal Jubilee Hospital in Victoria & Nanaimo Regional Hospital), & one in the North (Prince George Hospital) with St. Paul's being the referral site for the most complex patients; Prince George has funding to implant IT pumps only, not SCS
- One pain program (in Fraser Valley) is interested in exploring the possibility of offering neuromodulation
- SCS, intrathecal pump therapy, and PNS are provided through the existing pain programs with SCS being the most frequently implanted technology
- In the past year approximately 40-45 neuromodulation devices were implanted in new patients, the majority of these being SCS (i.e., 35 to 40)
- There are approximately 400 patients living with neuromodular implants currently being supported through these programs (Vancouver Coastal - ~260; VIHA - ~90; Northern - ~55)

16.1 Neuromodulation across British Columbia

Four pain programs in BC currently offer neuromodulation as a treatment option: The St. Paul's Complex Pain Program in Vancouver, the Royal Jubilee Hospital Pain Program in Victoria, the Nanaimo Regional Hospital Pain Program, and the Prince George Pain Program (Table 22). Of these, only St. Paul's is affiliated with a neurosurgeon that completes device implantations. It has the largest pain program and receives referrals from across the province. SCS and intrathecal pump implants are being done by specially trained anesthesiologists across the other pain programs. PNS is also performed through St. Paul's primarily for refractory headaches. The program that currently does the 2nd highest number of neuromodulation implants is the Nanaimo Regional Hospital's pain program, followed by the Royal Jubilee Hospital in Victoria's pain program and the Prince George pain program. A large, multidisciplinary pain program at the Surrey Hospital in the Fraser Health Authority expressed interest in exploring the possibility of adding neuromodulation as a treatment option.

Table 22. Chronic Pain Neuromodulation Treatment Interventions in BC

Site/ Location	Pain clinic description	Types of neuromodulation provided & for what conditions	Infrastructure & funding	Trial process	Wait times for neuromodulation
Vancouver Coastal – St. Paul’s Complex Pain Program	Multidisciplinary pain clinic (2 FT nurses; 1 neurosurgeon; 2 pain physicians (anesthesiologists);	<ul style="list-style-type: none"> - SCS for FBSS, CRPS, neuropathic pain (e.g., post amputation, brachial plexus rupture, diabetic neuropathy), refractory angina, peripheral vascular disease - Peripheral nerve stimulation, primarily for refractory headaches - Intrathecal pumps for Ca pain; don’t implant for non-Ca pain, as just don’t have the resources 	<ul style="list-style-type: none"> - No fluoroscopy suite - OR time (4 days/month) - Pain program equipment budget now under surgical ambulatory clinic, so uncertain about # of devices funded 	<ul style="list-style-type: none"> - 1-3 week long trials done in the OR - Do 50/50 percutaneous & permanent trials - Of the patients who start through the selection protocol – at least 50% would go on to a trial - Of the patients who go to trial, 80-90% go onto a permanent implant 	<ul style="list-style-type: none"> - ~ 4-6 months for a consult - ~6-12 mos. for SCS for FBS; trying to get wait for CRPS down to 3 mos. - Also depends on physician availability, & whether a neurosurgeon is needed - WCB patients can wait longer
Vancouver Island-Nanaimo Regional Hospital Pain Program	Multidisciplinary pain clinic (3 pain fellowship trained anesthesiologists, part time PT, OT, SW, psychology, pharmacy, 3-4 nursing staff, admin staff); ~30 patients/day	<ul style="list-style-type: none"> - Primarily do SCS, usually for FBSS or CRPS - Rarely do an intrathecal pump for Ca pain 	<ul style="list-style-type: none"> - Fluoroscopy suite, where they can do most trial implants - OR time (1 day every two months) – 50% of procedures are for revisions - Funded for 13 implants/yr. for all of the Island of which they do ~8/yr. 	<ul style="list-style-type: none"> - 3 weeks long percutaneous trials, usually in the fluoroscopy suite 	<ul style="list-style-type: none"> - Currently don't have a 'wait list' - More recently, our longest wait has been ~5 months - There is ~ a 3 month wait to get into the pain rehab program, but new pain, where some intervention is likely to help - including NM, will skip that wait
Vancouver Island-	Multidisciplinary pain clinic	<ul style="list-style-type: none"> - Primarily does: SCS for FBSS & refractory angina 	<ul style="list-style-type: none"> - Fluoroscopy suite - OR time (2 half-days) 	<ul style="list-style-type: none"> - Do permanent lead trials for 	Not reported

Victoria (Royal Jubilee Hospital) Pain Program		<ul style="list-style-type: none"> - Does not do SCS for CRPS, instead do neurolysis with hypertonic solution (Racz procedure) - Occasionally do peripheral nerves implants for occipital neuralgia - No intrathecal pumps due to the lack of infrastructure support 	<ul style="list-style-type: none"> - per month)¹ - OR team includes: anesthesiologist doing the implant; 2 OR nurses; 2 pain clinic nurses; 1 manufacturer rep. - Funded for 13 implants/yr. for all of the Island of which they do ~5/yr. 	<ul style="list-style-type: none"> - SCS for FBSS², so do them in the OR - Have a 20% failure rate (i.e., about 1 in 5 do not proceed to a permanent implant) 	
Northern Health - Prince George Pain Program	Pain clinic, but not multi-disciplinary (2 pain physician anesthesiologists, one who is retiring soon; 2 nursing staff); ~60 patients/wk.	<ul style="list-style-type: none"> - Do intrathecal pumps, & primarily for non-Ca pain - Every year implant a couple of pumps for intractable Ca pain 	<ul style="list-style-type: none"> - Challenge to get funding for pumps every year. - No funding provided for SCS. - Have adequate x-ray time, OR time - Works closely with general surgeon to do implants 	<ul style="list-style-type: none"> - Didn't discuss - Knows patients very well; only consider pump implants for those patients where they have tried everything else 	<ul style="list-style-type: none"> - 3-year waiting list for pumps - Have referred a few patients to St. Paul's for a SCS, but many find it hard to travel to Vancouver
Surrey Hospital pain program	Multidisciplinary pain clinic (8 pain doctors – 6 anesthesiologists, 1 orthopedic surgeon, 1 physiatrist, allied health – PT, OT, SW, nursing, psychology); ~2000 patients/mo.	<ul style="list-style-type: none"> - Not currently providing neuromodulation, but do have an interest in adding this as a treatment option - Refer patients to St. Paul's 	Have a procedure room, and do everything except for NM (e.g., radio-frequency lesions, medial branch blocks, epidural injections, epidural lysis, nerve root blocks, etc.)	n/a	n/a

¹This OR time is for any procedure that required a more prolonged recovery time that can be supported in an outpatient clinic setting (ketamine infusion, Racz procedure to shrink epidural fibrosis). NM techniques compete with these other interventions for pain for surgical time.

² Because most patients tend to go onto a permanent implant, Victoria uses permanent leads in their trial stage. Have OR time the 2nd and 3rd half-Mondays. Do the trials on the 2nd Monday and are programmed with an exterior program device; then if the trial is successful, they have the temporary extender taken out and the placement of the implant is a relatively short procedure.

16.2 Types of Neuromodulation and their Indications

SCS is by far the most common kind of neuromodulation currently being done in BC for pain, and is done for the following conditions, in order of frequency: neuropathic pain post failed back surgery, CRPS, refractory angina (post cardiac bypass or for those not eligible for bypass), and other kinds of chronic neuropathic pain. The patient population receiving SCS is split approximately 70/30 between failed back surgery and all other eligible pain conditions. The second most frequently employed neuromodulation treatment is implantation of intrathecal pumps, both for cancer and non-cancer pain. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 23. Neuromodulation implant and revision details by pain program

	Neuromodulation Technology										~Number of pts with implants being supported
	Spinal Cord Stimulation (SCS)		Transcutaneous supraorbital nerve stimulation (tSNS)		Peripheral nerve stimulation (PNS)		Peripheral nerve field stimulation (PNFS)		Intrathecal Pumps		
	New implants	Revisions	New implants 2017-18	Revisions	New implants 2017-18	Revisions	New implants 2017-18	Revisions	New implants 2017-18	Revisions	
Vancouver Coastal – St. Paul’s Complex Pain Program	22 (in 2017/18)	34 in 2017/18)	0	0	0	0	0	0	3 (Ca)	4	220 SCS ~40 intrathecal pumps
Vancouver Island- Nanaimo Regional Hospital Pain Program	6-10 yr. for FBSS & CRPD	unknown	0		0	0	0		2-3 (Do for Cancer pain only)	unknown	90 (both SCS & pumps)
Vancouver Island- Victoria (Royal Jubilee Hospital) Pain Program	4-5/yr. for FBSS 2/yr. for angina	unknown	0	0	1-2/yr. for occipital neuralgia	?	0	0	0 over past 3-4 yrs (do purcutaneous catheters)	unknown	unknown
Northern Health - Prince George Pain Program	Refer to St. Paul’s	0	0	0	0	0	0	0	~6-7/yr. (Mostly non-Cancer; 1-2 Cancer per yr.)	unknown	55
Interior – no publicly funded multi-disciplinary pain program	Refer to St. Paul’s	0	0	0	0	0	0	0	0	0	0
Fraser Valley – Surrey Hospital Pain Program	Refer to St. Paul’s	0	0	0	0	0	0	0	0	0	0
Totals	32-37				1-2				12-14		405+

17 Key Informant Interviews: Health Professionals

Summary

- Thirteen BC health professionals participated in in-depth telephone interviews
- Clinical experience in BC is that:
 - Neuromodulation is highly effective for specific sub-groups of patients, making the assessment & trial processes an important component of neuromodulation programs
 - BC programs experience a 80-90% success rate, defined primarily as improved function & quality of life, & decreased pain
 - Neuromodulation is best embedded in a multi-disciplinary pain clinic/program
- Neuromodulation is a rapidly evolving field both with respect to the technology itself, & in the understanding of how neuromodulation for pain works & for which types of pain it will be most effective
- Pain BC has worked with the BC Ministry of Health to develop a pain strategy for BC
- There are some current challenges with neuromodulation, both with respect to sustainability & any potential growth

17.1 Purpose

To understand the British Columbia experience with neuromodulation for chronic pain (cancer and non-cancer), including: the patient population being treated with neuromodulation, patterns of care, perceived benefits and challenges, and current as well as potential future capacity to implement neuromodulation as part of a comprehensive pain strategy in BC.

17.2 Methods

Telephone interviews were conducted with a purposive sample of health care professionals. A snowball sampling approach was taken whereby health professionals who agreed to be interviewed were asked to identify other potential participants for this study. An effort was made to speak with individuals from each of the five health authorities.

A semi-structured interview guide was developed to support the interview process. This guide included questions on: the pain programs, current patterns of neuromodulation practice, perceived benefits and challenges, and insights into the future of neuromodulation in BC. The guide evolved over the course of the interviews, as questions were refined to reflect what had been learned through the previous interview(s). All interviews were conducted by an experienced qualitative researcher, audiotaped with the consent of the interview participants, and detailed notes were taken. The data were qualitatively analyzed using constant comparative analysis to

develop a picture of the BC context, and identify key themes related to the policy questions being posed.

17.3 Findings

17.3.1 Participants

Twelve telephone interviews were conducted with 13 BC health care professionals in April and May 2018; in one case two people were interviewed together. The interviews ranged in length from 40 to 90 minutes. Participants included pain physicians and anesthesiologists (n=6), neurosurgeons (n=2), pain clinic nurses (n=2), a pain physician and physiatrist (n=1), and an outpatient surgery manager (n=1). One interview was conducted with a member of Pain BC's senior management team. Five of those interviewed were affiliated with the Complex Pain Program at St. Paul's Hospital in the Vancouver Coastal Health Authority, two were affiliated with the chronic pain program at Surrey Hospital in the Fraser Health Authority, two were affiliated with the Nanaimo Regional Hospital Pain Program and two were affiliated with the Royal Jubilee Hospital Pain Program in the Vancouver Island Health Authority, and one was affiliated with the Prince George pain program in the Northern Health Authority.

17.3.2 Neuromodulation as a component of pain programs

Neuromodulation is a very small part of the practice of all the pain physicians interviewed. It is an intervention provided to a select group of patients that undergo a thorough assessment process and an implant trial, before a permanent implant is completed. Pain physicians describe neuromodulation as:

“One of the better evidence-based treatments available for a select group of patients with severe chronic pain; for the right patient, this is a very good treatment.”

Where neuromodulation fits in the patient care pathway appears to be evolving. Most physicians described it as the last treatment option considered, a patient will spend years living in pain trying to access an effective treatment prior to being assessed for neuromodulation. As understanding from research and practice has improved the identification of patients most likely to benefit from neuromodulation, physicians providing neuromodulation are suggesting that it can be moved further ahead in the care pathways. One physician noted that the placement of neuromodulation in a care pathway varies internationally. For example, in the European stepwise

treatment ladder neuromodulation comes before opioids, whereas in North America opioids precede neuromodulation.

17.3.3 Patient selection and clinical practice guidelines

Health professionals providing neuromodulation described use of a thorough and multi-disciplinary screening and assessment process to determine whether a patient is likely to benefit from treatment. This was particularly true for spinal cord stimulation. A number of physicians described a meeting held in 2013, where many people came from across Canada to work through development of the appropriate process. It was agreed that a team composed of at minimum a pain physician, a neurosurgeon, a psychologist should be involved to ensure optimal patient outcomes. Ideally the team would also include a physiotherapist, an occupational therapist, and a pharmacist.

Given this history, there was a lot of commonality in the selection protocols described by the individuals interviewed. Participants noted that the selection criteria continue to evolve to reflect their ongoing learning through both research and practice. Current patient selection criteria outlined by the interviewees are summarized in Box 2.

Box 2. Patient Selection Criteria for Neuromodulation

Inclusion criteria: Does or has the patient...

- Exhausted all other appropriate pain management strategies, including further surgery
- Have the kind of pain likely to benefit from a spinal cord stimulator, which was described as neuropathic (i.e., FBSS, radicular pain, neuropraxia, CRPS) or vascular (i.e., angina, peripheral vascular disease)?
- Have a pain distribution likely to benefit from SCS, with unilateral leg pain being the #1 indication?
- Understand pain and how to manage it?
- Understand that the device is to support pain management, not get rid of the pain entirely?
- Completed an education program that includes how to use the neuromodulation device, prior to the start of a trial?
- Agree to the contract, including the restrictions re when they can use the device?
- Have an implant trial that is a clear success (i.e., have at least a 50% decrease in pain plus an

improvement in function; and with intrathecal pumps – also at least a 50% decrease in opioid use)?

Exclusion criteria: Does the patient have...

- Have a kind of pain that is unlikely to respond to SCS (e.g., fibromyalgia, mechanical lumbar pain, epidural fibrosis), or be helped by an intrathecal pump?
- An untreated or unstable psychiatric condition
- An active, untreated addiction (e.g., drugs, gambling)
- An active infection
- A life expectancy of less than 3 months [this was noted with respect to intrathecal pumps for cancer pain]
- An inability to maintain and use the device

There is evolving discussion about the nuances related to the psychological assessment component of the screening and assessment process. Currently, if patients have end stage cardiac or cancer pain, a full psychological assessment is not necessary. One pain physician noted that the interventional pain service at Toronto Western Hospital's comprehensive integrated pain program is currently doing a pilot study, in which patients who are below the threshold on certain questionnaires and a screen for psychiatric disorders are not seen by a psychologist. Early findings from this study were presented at the North American Neuromodulation Society meeting in January 2018 and indicate that screening using validated questionnaires, along with the use of a checklist, may reduce requirements for a formal psychological interview. The lead author of this study, Dr. Anuj Bhatia, emphasized that currently the standard of care remains that every patient deemed appropriate for a SCS trial should participate in a psychological interview. Given that a full psychological assessment is often the rate-determining step in getting through a pre-trial screening process, this kind of research is seen as highly valuable.

Many of the pain physicians emphasized they believe there is a strong body of research evidence supporting the use of SCS for failed back surgery with unilateral neuropathic pain, so many of them prioritized these patients for trials – given the scarcity of resources. They also noted that recent RCT's have shown cost effectiveness of neuromodulation for certain kinds of pain, and that the research just isn't able to keep up with the rapidly evolving technology. When asked

specifically about clinical practice guidelines followed in their practice, pain physicians referred to those posted on the International and North American Neuromodulation societies' websites. As one physician stated:

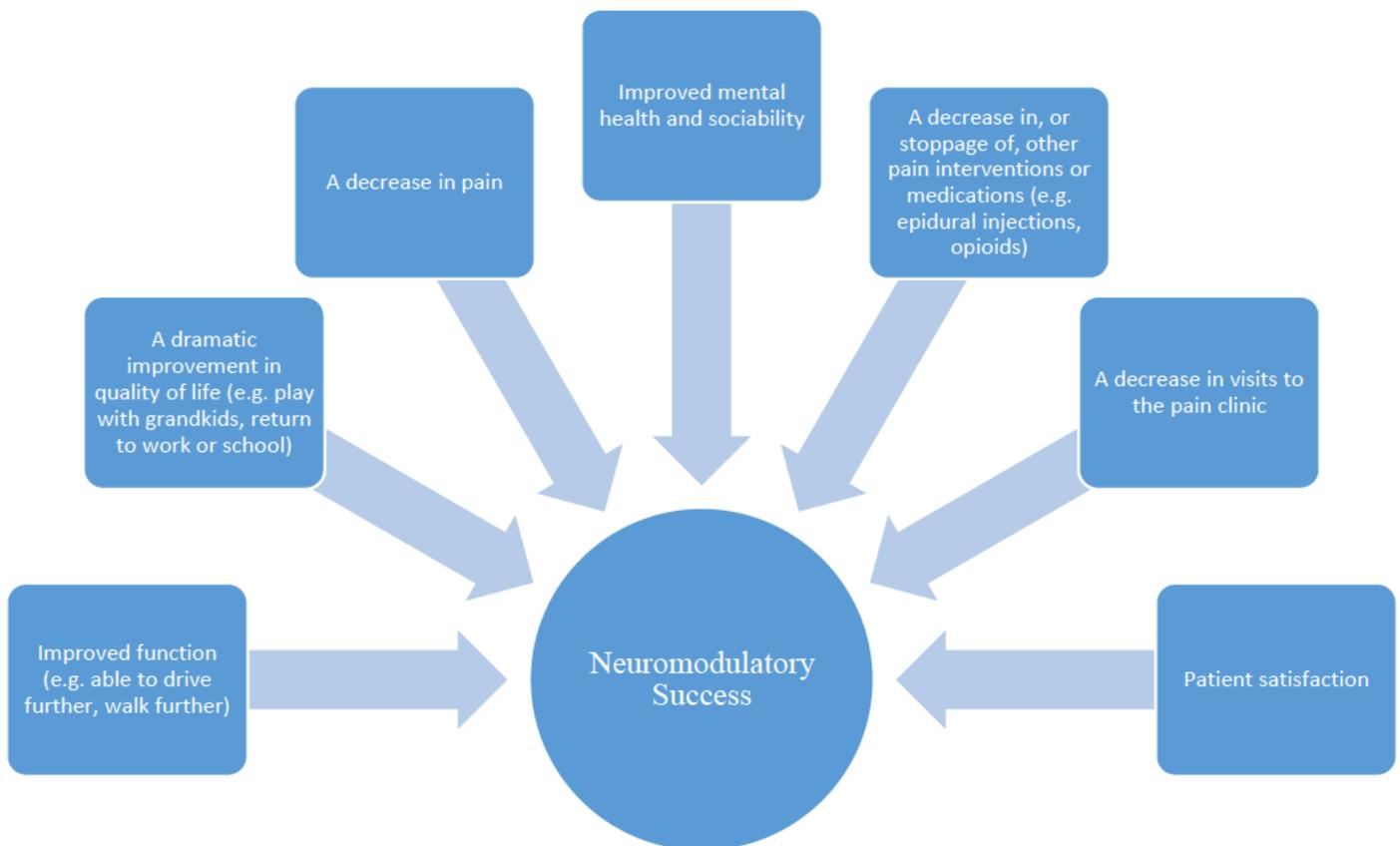
“Everyone in the field, which is very small, sticks with the same guidelines.”

One guideline was referenced by interviewees.³² A textbook on neuromodulation used in pain medicine fellowship programs was also referenced.

17.3.4 Defining the success and effectiveness of neuromodulation

Healthcare professionals were asked how they would define success for neuromodulation treatment. The criteria stated most frequently are summarized in Figure 13.

Figure 13. Defining success of neuromodulation treatment



With respect to their experience with effectiveness, interview participants indicated that if patients are selected using appropriate criteria, including going through a rigorous trial, then treatment is very effective. As one pain physician said:

“It’s hugely successful for a small group of carefully selected patients.”

Programs providing neuromodulation described their success rates at 80-90%. Health professionals noted:

“[there is] a day and night change re pain and disability for those patients for whom it works...; that is why there is a trial before you do the implant, as you can clearly see whether it will make a difference for this patient”.

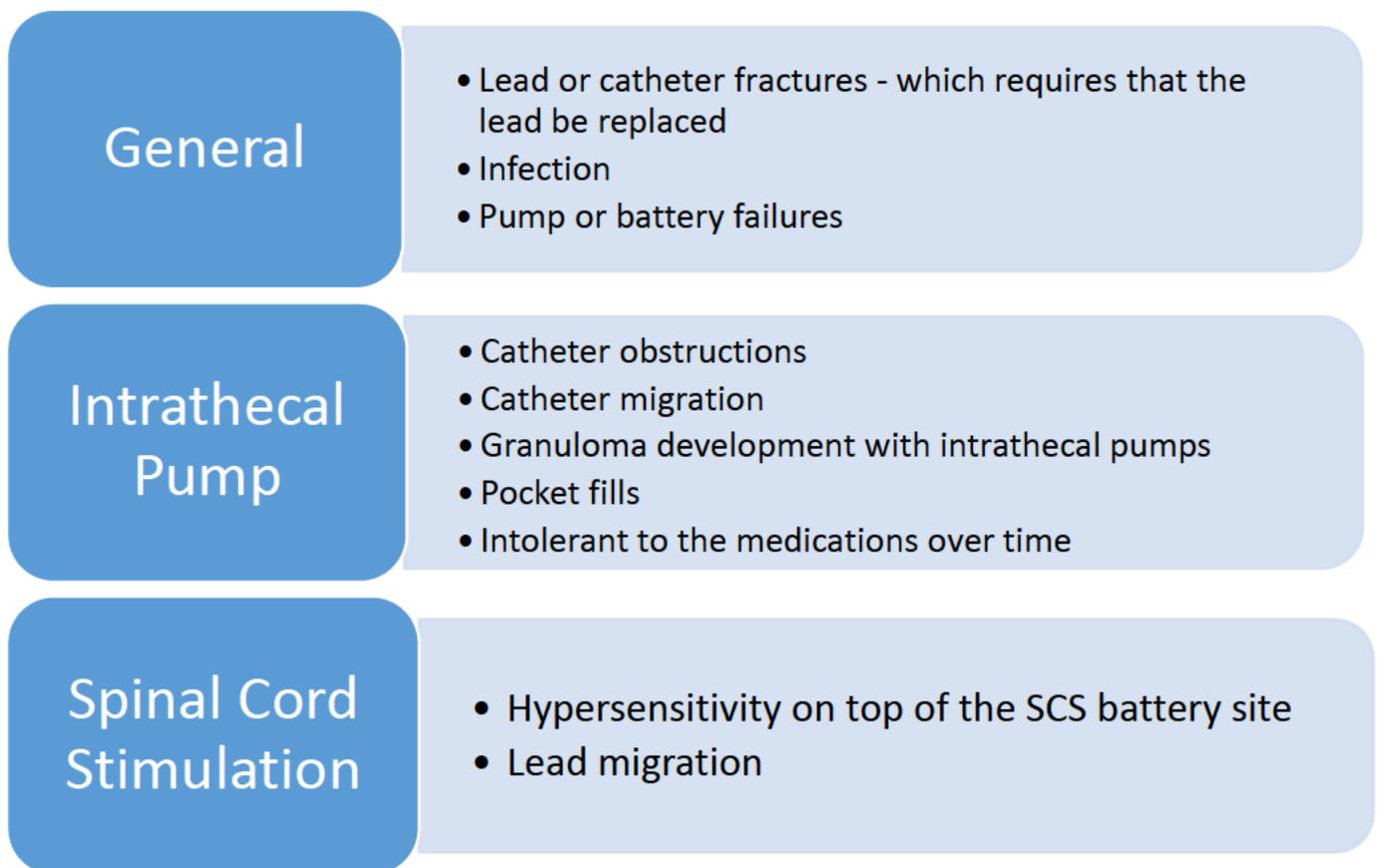
Others described it as one of the few non-medication based treatments for chronic pain that is “life altering”. Informants described many examples of people being able to dramatically decrease or altogether discontinue their pain medications and being able to do so much more (i.e., walk much further, drive for longer periods of time, go back to work), overall experiencing a more enjoyable and fulfilling life.

Many said that they believed there were savings to the healthcare system as people were not using as many other services. That is, they come in for fewer pain intervention procedures, have fewer visits with the pain clinic and their family doctor, use fewer pharmacare dollars, and/or have fewer admissions to emergency departments. One informant said that at their site some patients with implanted devices come for small procedures, but that the goal is to replace these. Currently, around 20% may come back for other interventions and 80% do not. Others commented that it was challenging to make an economic case for government as many of the cost savings do not return to the Ministry of Health, but to the government and society more broadly. For example, the dollars saved from patients and/or spouses who are able to go back to work go to treasury.

17.3.5 Complications

Participants noted that the main complications of neuromodulation implants are well documented in the research literature, and that their own experience mirrors this. The main complications of SCS and intrathecal pump implants interviewees described are summarized in Figure 14. Significant neurological complications were described as extremely uncommon.

Figure 14. Common Neuromodulation Complications



Participants noted an increase in potential complications and risks with intrathecal pumps compared with SCS. Pain physicians indicated they required more ongoing care including refills every few months. One pain physician commented that there was a quantum leap in term of risk going from a SCS to an intrathecal pump. These comments highlighted the need for satisfactory infrastructure to support intrathecal pumps as they require extra maintenance, vigilance, and attention to detail.

17.3.6 The future of neuromodulation

Interview participants described neuromodulation as a rapidly evolving field with respect to the technology itself. There is also an increasingly sophisticated understanding of how neuromodulation for pain functions and for which types of pain it will be most effective. As one physician noted:

“There is a lot changing, it’s a growing field...learning about new indications and new ways of treating pain by changing parameters.”

A description of current changes and developments, described by interview participants, is provided in Box 3.

Box 3. The Evolution of Neuromodulation Technology

- Batteries are now rechargeable, meaning they have a longer life
- The sizes of the batteries are decreasing, and this means both that the surgery site gets smaller and the implant is more comfortable for the patient
- There is early work being done on developing version of devices, where only the wire is implanted in the body and the stimulator is kept outside the body
- The actual programming has undergone tremendous evolution in the past 5-10 years, and this is ongoing
 - There are new ways of treating pain by changing parameters, and more ways of manipulating the current
 - Software allows for modification of the electrical field, and where it can best be directed to improve the coverage
- Higher frequencies are becoming available, including new technology with very high frequency that will cover central back pain, and ultra-high frequency burst technologies.
- There are more options being developed for the kinds of leads available
 - Longer leads, so even if you get a migration, it isn’t as big of an issue as they are able to cover a bigger area with one lead
 - Leads with more contacts, meaning you may not have to revise patients as much
 - Thinner leads that you slide along a particular nerve route – and you can keep it in place easier with little ‘tines’
 - Dual leads
- There are new anchor devices
- The information able to be stored on the device is improving (e.g., can now store

images)

- This may make it easier for patients to be followed and supported closer to home
- Peripheral nerve stimulators are evolving, and peripheral nerve stimulation is seen as an option for more kinds of pain
- Dorsal root ganglion stimulation is a newer technology that is good for certain kinds of neuropathies (i.e., more focal pain, post abdominal trauma pain, post inguinal surgery neuropathic pain)

Some key informants noted that it's becoming increasingly recognized that for some pain syndromes neuromodulation should be considered the first and best intervention. Pain physicians talked about research done by Dr. Chris Kumar comparing early to late access to neuromodulations for patient who are good candidates, with early access (6 months to a year), resulting in earlier return to work and improved functioning. Repeat surgeries are actually the wrong thing to do; that is you don't want the person to go through repeated surgeries that are not likely to help before finally considering neuromodulation as an option). So earlier intervention is better than late intervention, for those patients who have the kind of pain that can be helped with neuromodulation. One experienced pain physician made the point that although not every neuromodulation patient is a success story, neither is every back surgery patient.

“Millions and millions of dollars are spent on back surgery, and a significant proportion of these have a very poor result”.

The current lack of access to neuromodulation, then, was described as having a potentially huge, negative impact on people living with pain. Finally, with the opioid crisis, and a focus on “trying to reign back the use of opioids”, neuromodulation is increasingly being considered for the select group of patients for whom this is a good option. All of these factors are contributing to a growing demand in BC which is not being met.

17.3.7 Challenges with providing neuromodulation treatment

As described previously, the experience in BC is that neuromodulation is a highly effective treatment option for a select group of patients living with severe, life-altering chronic pain. There

are currently only a few hospital-based pain programs in BC able to offer neuromodulation as an option to the select group of patients likely to benefit. The main challenge with sustaining, and potentially increasing access to neuromodulation treatment as part of a range of treatments and other supports available for people living with chronic pain, is the funding and infrastructure available. This means that currently access for patients likely to benefit is often restricted.

To optimize effectiveness, many of these key informants suggested that neuromodulation treatment needs to be embedded in a hospital based or aligned multi-disciplinary pain program and needs to include appropriate funding for all members of the team, the equipment (i.e., the SCS devices, the intrathecal pumps, the leads and catheters), fluoroscopy suites and/or operating room time. Many people noted the lack of OR time available as a challenge: “*Access to OR time is like gold*”. One pain physician commented that open procedures, or anything that requires a longer recovery due to potential problems with hypotension and/or delirium, cannot be supported in a fluoroscopy suite or procedure room in a pain clinic. There is not the staffing, nor the space, needed to recover these patients properly within a pain program space.

Capacity is required to support patients who are living with implanted neuromodulation devices. Many people commented on the need for additional nursing staff to support this population of patients. These patients also require revisions, including new implants when the batteries expire. All of the physicians doing implants said that they spend at least half of their time doing revisions on current patients, rather than doing initial implants on new patients. Although some equipment is funded through other budgets (i.e., pumps are funded through the BC Cancer agency; implants for angina are funded through the provincial cardiac program), these budgets only cover the equipment and none of the infrastructure costs.

A number of individuals described a move away using intrathecal pumps for pain management, citing a number of reasons for this trend, including:

- They are more difficult to manage. If a pump malfunctions, or stops functioning or stops working, it can be lethal – either due to an overdose or severe withdrawal.
- There is no on-call stipend for people who deal with intrathecal pumps. As one physician stated: “If I put an intrathecal catheter in palliative care ward, and they have a pump failure and are in a pain crisis, I have to be available 24/7. Why would physicians do this? You only do this, as you have an idea of the profound changes it can make to patients.”

- With the advent of Medical Assistance in Dying (MAiD), some pain physicians are seeing a decrease in requests for pumps for intractable cancer pain.

Regardless, many pain physicians felt that intrathecal pumps will continue to be the best option for a select group of patients for both cancer and non-cancer pain, but with evolving technology the size of this group is expected to decrease. More infrastructure support would help increase access for this select group of patients to intrathecal pumps. In some places, such as Victoria, they are moving to doing more percutaneous or temporary catheters for pain management in cancer patients.

Finally, many key informants stated that the initial cost of the device has always been a restriction from a pain point of view, and that government's reluctance to pay for the device is an issue in many places across Canada, including BC. Specific needs to sustain and potentially increase capacity are described in more depth in the following section.

17.3.8 Sustainability and increasing capacity in BC

Many participants emphasized that more than increased funding in equipment would be required to support increased capacity for neuromodulation in BC and to make it more accessible for people living with pain. As one key informant said:

“There is a need to fund infrastructure to support NM implants; we could work better with the same amount of equipment funding”.

Better infrastructure would enable the pain programs: to see patients who are likely to be good candidates more quickly, to optimize the selection of patients before the device trial process, and to optimally support patients living with an implant. The infrastructure required to optimally support neuromodulation are summarized in Box 4 with additional discussion below.

Box 4. Infrastructure Requirements

- More dedicated OR time and OR nurses
- Funding for a fluoroscopy suite to do trials, which will free up OR time for permanent implants
- More multi-disciplinary team funding (e.g., psychology, PT, OT, SW)

- Additional nurses and more training available for nurses
- Full time manager dedicated to the pain program at St Paul's
- More neurosurgeons [specifically a 2nd neurosurgeon based at St. Paul's]
- More pain physicians trained in neuromodulation
- Increasing the fees paid through MSP for doing trials, permanent neuromodulation implants and revisions.
- Need a budget that incorporates revisions and replacements [just like in cardiology for pacemakers]; currently, a battery change or a pump change, its considered to be a new device – and comes out of a limited equipment budget

Having a nurse dedicated to supporting patients with neuromodulation implants, particularly for the larger programs, was identified by a number of key informants as important. Better access to training for nurses, was also mentioned. Nurses have a number of important roles to play in supporting an effective neuromodulation program, including: being heavily involved in the process leading up to a trial, making follow-up calls to patients, equipment ordering, maintaining a data base. Much of the ongoing support for patients, including the education on pain and pain management, is done by nurses. This education piece is described by many as an important foundation of neuromodulation, given that it is a pain management tool and not a cure for people living with chronic pain. Not enough nursing support will limit the number of implants that can be done per year. Nanaimo, for example, used to do 25 new implants a year, but due to a lack of funding for nursing support this could not be sustained.

Some key informants felt that it would it might be worthwhile to consider having someone working with the psychologist to extend that role. That is, doing all the screening, pain scales, etc. with patients pre and post implant, and ongoing assessment. This would ensure that the psychologists time is focused on doing more thorough pre-trial assessments, when indicated, and providing ongoing counselling where necessary.

With respect to the kind of additional training a pain physician (e.g., anesthesiologist, physiatrist) would require to be able to start providing some neuromodulation treatment it was suggested that someone who had a pain fellowship and/or was already doing a lot of interventional pain procedures wouldn't need a lot of training above and beyond that. Providing some

neuromodulation treatment as well is just going one step further. Additional training required could likely be supported at St. Paul's or Nanaimo, just by working with people there, for a period of time. Currently, neuromodulation is not a core part of pain fellowship programs in Canada, although physicians usually have the option of doing some neuromodulation if they have an interest. The neurosurgeon at St. Paul's has been involved in training residents interested in neuromodulation, and he would be interested and has the capacity to do more procedures and do more training and mentoring.

There also needs to be effort made to increase physician and particularly neurosurgeon awareness of neuromodulation as a treatment option, and how to refer patients. As one physician said:

“There is a general lack of awareness of how effective NM can be for certain kinds of pain.”

This lack of awareness includes: the public, referring physicians, and pain specialists. So doing this education is critically important, so that there is an increase in awareness about NM as an option.

A major issue described by all the physicians, both anesthesiologist and neurosurgeons, currently doing neuromodulation implants is the lack of compensation provided through current fee codes; and for some procedures such as intrathecal pump filling and some types of revisions there is no code at all. Some physicians noted that they made less money on the days that they were doing implants, with anesthesiologists stating that they got paid more for far simpler intervention procedures such as trigger point injections. As one physician stated:

“Most neurosurgeons just become spine surgeons, as it's far easier and more lucrative.”

This makes it challenging to sustain the amount of neuromodulation currently being provided and prevents increasing capacity. When asked why physicians do neuromodulation, when it is so poorly re-numerated, the response was that they “love to see the benefits”, in that for some patients living with chronic pain it is a life-changing treatment.

“If you can give patients something that will both decrease their pain and improve their quality of life, then you want to do that.”

Ultimately this affects sustainability, as it makes it challenging to make neuromodulation appealing for few neurosurgeons and anesthesiologists who are looking at the most efficient use of their time. For example, doing SCS implants pays less than half of spinal surgery. Funding mechanisms that attract, rather than deters physicians, from this field would be helpful. As one physician stated:

“There is currently no incentive at all for doing neuromodulation, more disincentives. So future is not spectacular, as money is the driver... If incentives were there, and procedures appropriately funded, could get more physicians interested – but they also need the passion for working with chronic pain patients.”

17.3.9 A hub and spoke model

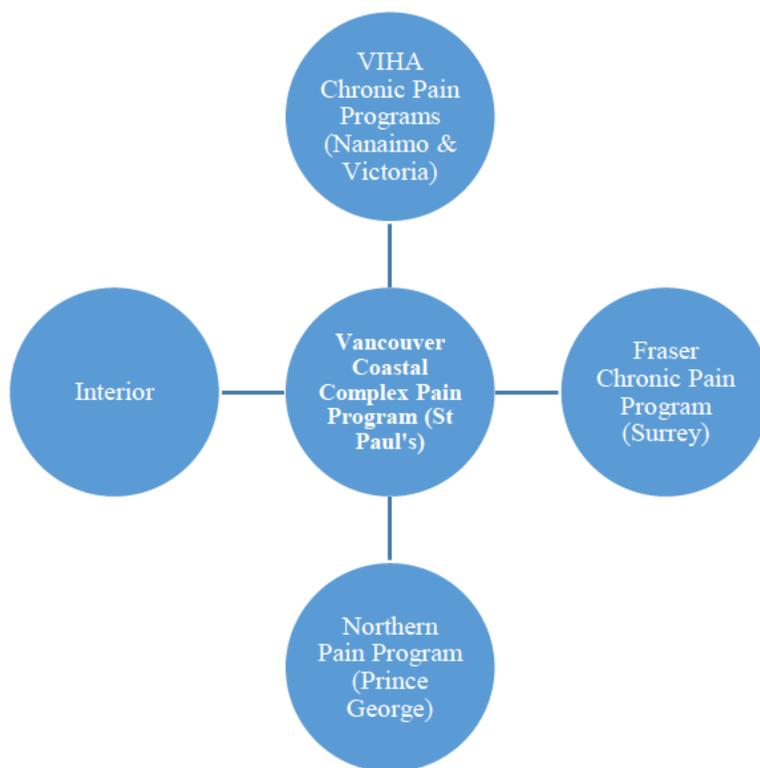
Many key informants describing organizing this needed infrastructure into a provincial neuromodulation program, which they saw being structured as a hub (i.e., center of excellence) and spokes (peripheral sites) model (see Figure 15). Other highly specialized surgical programs in BC currently operate using this kind of a model. This type of model is felt more likely to be sustainable than having everything flow through this one center. It was stressed that these sites need to be connected in a single provincial program.

St. Paul’s Hospital Complex Pain Program was described by all as the hub of such a model and is currently informally acting in this capacity. Currently, health authorities who do not offer neuromodulation refer their patients to St. Paul’s. Programs doing neuromodulation also refer their more complex patients to St. Paul’s, including when a SCS implant requires a surgical vs. a percutaneous lead (i.e., Nanaimo, Victoria). Prince George refers any patients who many benefit from a SCS to St. Paul’s, as currently they only have funding to implant intrathecal pumps.

In this model, each health authority would either provide neuromodulation for less complex patients and be able to provide some support to their patients ‘closer to home’ through, for example, being able to do intrathecal pump refills, do some trouble-shooting for neuromodulation implants, and be able to continue to support patients with adjunct pain management strategies. Neuromodulation would be provided as one option integrated into a multi-disciplinary chronic or complex pain program. Many patients require ongoing support to optimize their pain management, even with an implant. Also, for those patients who are not eligible for an implant, other kinds of treatments and supports should be available (e.g., exercise,

psychology). Referrals to this neuromodulation program would come from a variety of sources, including: primary care practitioners, other smaller pain programs, neurosurgeons, other specialists, BC Cancer Agency programs and WCB.

Figure 15. Possible Provincial Neuromodulation Program- Proposed Hub and Spoke Model



Some spoke specifically about the importance integrating both clinical and academic research into this provincial program, so that there is the potential to both increase access to and generate new knowledge. People working in this field want to collect useful data in order to help validate the benefits to patients that they are seeing. There is interest in developing a provincial neuromodulation registry, and currently the Vancouver Island sites are actively working on updating their local registry. Some said that a mechanism is also needed to report on and assess new technologies, given this is an evolving field; with one pain physician specifying that HTA's are helpful here, as long as people continue to do the research.

Other Canadian neuromodulation programs that may be consulted with to usefully inform the development of a BC program are the program in London, Ontario led by Dr. Andy Perrant and the program at Toronto Western Hospital. Finally, one pain physician said that all of the clinicians are working flat out, due to a lack of funding and strategy.

“It would be good to sit down at a table and figure out what we really want”.

17.3.10 Neuromodulation as part of a bigger provincial pain strategy

Many said that ideally the neuromodulation program should to be part of a bigger provincial pain strategy. Two key informants noted that there is a gap between what Pain BC can offer in terms of self-management and what can be done through primary care, and what can be provided through a multi-disciplinary pain program for those people who continue to struggle. As one pain physician noted, many people living with chronic pain are unable to work, making it difficult to pay for physiotherapy, psychology, and other allied healthcare professionals’ support that is not funded through BC Health. To address this unmet need, private pain clinics are springing up.

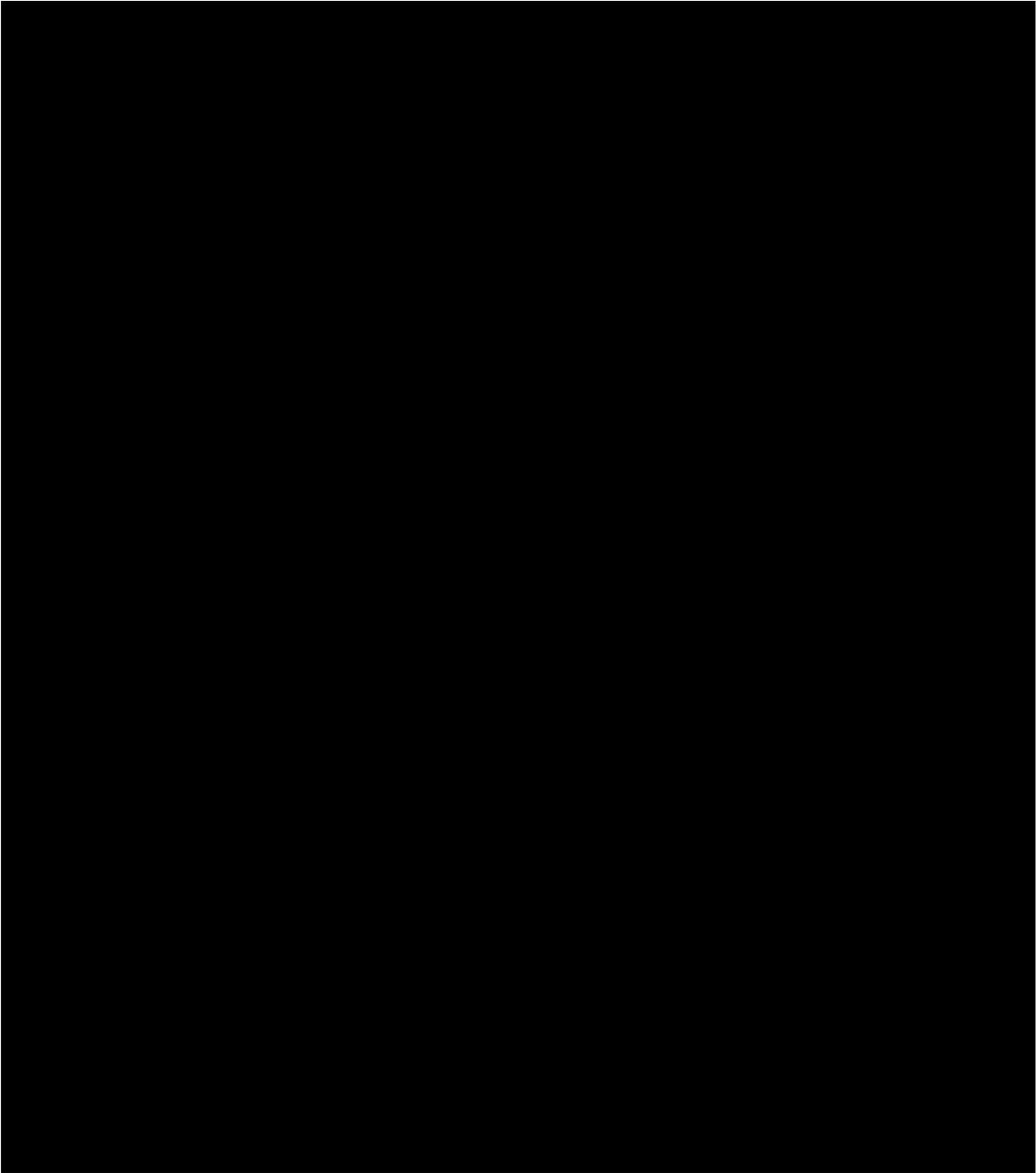
Pain BC’s mandate is to improve lives of people living with chronic (non-cancer) pain – this primary involves: advocacy work, healthcare professional training, and self- management support for people living with pain¹²⁰. The philosophy of Pain BC is: “Nothing about us without us”. People living with pain and their families are embedded throughout the organization; they sit on the Board, and on all of the committees [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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Pain BC is working closely with the BC Ministry of Health's Department of Chronic Disease Management and Primary Care to develop a provincial strategy for chronic, non-cancer pain that would address these barriers to accessing services; making the case that it would both save money and increase the quality of patient lives.

In addition to the tertiary complex pain program at St. Paul's, included in this strategy is a secondary tier that deals with complex pain in the different provincial regions. These secondary multi-disciplinary pain clinics would include addictions specialists to help address a current gap in treatment access. Patients struggling with addiction are often not accepted in hospital-based, tertiary pain programs, as they need to have their substance abuse under control before they will be seen. This fits with the hub and spoke model for neuromodulation that was described by a number of key informants working in tertiary and secondary pain programs. There is also a move toward the development of primary care networks in BC, which will incorporate the development of "medical homes". Some of these PCNs may develop a focus on supporting patients living with moderately severe chronic pain and functional limitations. Pain BC has also recently announced a partnership with UBC to develop a pain research network.¹²²

Neuromodulation is seen as a highly specialized service that will require support from a tertiary hub. There is hope that some capacity can be developed in each region to support patients, at the very least, pre and post implant. That is, ensuring there is appropriate referral and patients can receive some follow-up closer to home, with the support of the "expert hub". Pain BC is actively exploring a model known as Echo,¹²³ to support the provision of care in remote areas. This model emphasizes both building local capacity and providing increasing access. The emphasis is on local case-based learning with support from specialist team at a hub. In this way the capacity of local providers and their patients grow. The need for this kind of an approach is mentioned in the provincial strategy.

17.4 Conclusion

Key informant interviews provided a rich description of the programs within which they worked, and where neuromodulation fit in the broader pain management picture. Neuromodulation is a very small component of the practice of pain physicians, but a pain management treatment that works very well for a small group of patients. A contributing factor to this is the thorough

assessment and trial process that patients go through prior to a permanent implant being provided.

The nurses and physicians working with these patients described neuromodulation as being life altering for many of them, in that they are able to do so much more with their lives. In addition, many believed there were savings to the healthcare system as these people were not using as many other services. That is, they come in for fewer pain intervention procedures, have fewer visits with the pain clinic and their family doctor, use fewer pharmacare dollars, and/or have fewer visits to emergency departments. This resonated strongly with what we heard from patients directly (see Section 20).

Neuromodulation is rapidly evolving with respect to the technology itself, and with respect to the understanding of how it works and for which kinds of pain it's likely to manage effectively. Yet there is still a lack of awareness amongst both healthcare professionals and people living with severe life-changing pain, about neuromodulation as a treatment option. This lack of awareness, along with the current lack of capacity in BC to provide neuromodulation, means that many people who could potentially benefit do not currently have access. There is a need to improve access to neuromodulation as part of well supported multi-disciplinary pain programs. In order to ensure that patients have access to this support as close to home as possible, consideration should be given to having at least one such program providing neuromodulation in each of the five BC regional health authorities, with St. Paul's program acting as a hub in a hub and spoke model.

18 Systematic Review of Patient Perspectives on Neuromodulation

Summary

- A systematic review of the published qualitative research on patient experience with neuromodulation for pain was completed
- A narrative synthesis approach was used to identify and understand the key findings from the five included studies
- Across these five studies, a total of 53 patients participated in one or more in-depth interviews
- The primary themes emerging across four of the five studies were: the individuality and complexity of the experience of living and coping with chronic pain; adapting to and using neuromodulation as a strategy for better managing pain; and, the positive impacts of neuromodulation with respect to both pain reduction and improving function and quality of life.
- A key theme emerging from the fifth study, was the importance of the patient-surgeon relationship as an influencing factor in a patient's comfort level with having their structural spine surgeon also perform the surgery to implant SCS device.

18.1 Purpose

To synthesize published literature on patient experience with neuromodulation pain.

18.2 Methods

18.2.1 Search Strategy

A systematic review was completed and four databases were searched: MEDLINE, EMBASE, PsychINFO, and all EMB reviews. Databases were searched from inception to March 19th, 2018. Terms aimed to capture the neuromodulation technologies of interest such as “neuromodulation”, “spinal cord stimulation”, “electric stimulation”, “intrathecal drug administration” were combined with the Boolean Operator “or.” These searches were then combined with terms to indicate the patient perspective such as “interview”, “qualitative research”, “patient satisfaction” and “focus group”. Terms were searched as textwords in titles and abstracts or as subject headings (e.g. MeSH). The search strategy was designed to limit results to human studies and to studies published in either English or French only. No other filters were used. The full search strategy can be found in Appendix O.

18.2.2 Study Selection

Abstracts were screened in duplicate by two reviewers. Records were screened and advanced to full-text review if they were: qualitative study designs that described adult patients' perspectives on spinal cord stimulation for cancer and non-cancer pain, transcutaneous supraorbital nerve

stimulation for non-cancer pain, peripheral nerve stimulation and peripheral nerve field stimulation for non-cancer pain, and intrathecal pumps for cancer and non-cancer pain; were published in English or French; and reported any outcome (e.g. patient outcomes, health system outcomes, or health care provider outcomes). Articles did not proceed to full-text review if they included patients under 18 years of age, were published in a language other than English or French, or if they were animal models.

Studies that were included by both reviewers advanced to full-text review, which was also completed in duplicate. The following inclusion and exclusion criteria (Table 24) were used to assess eligibility in full-text review. Discrepancies in included studies were resolved through discussion between reviewers or a third reviewer.

Table 24. Inclusion and Exclusion Criteria Patient Perspective Review

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Examines patient, family, close friends or caregivers perspectives on one of the following neuromodulation technologies: <ul style="list-style-type: none"> ○ Spinal cord stimulation of cancer or non-cancer pain ○ Transcutaneous supraorbital nerve stimulation for non-cancer pain ○ Peripheral nerve stimulation for non-cancer pain ○ Peripheral nerve field stimulation for non-cancer pain ○ Intrathecal pump for cancer or non-cancer pain • Adults over 18 years old • English or French language only • Any outcome • Qualitative study design 	<ul style="list-style-type: none"> • Under 18 years old • Animal models • Does not report original data

18.2.3 Data Analysis

A narrative synthesis approach was used to identify and understand the key findings from the included studies. This approach is commonly used to synthesize heterogeneous literature,¹²⁴ including qualitative studies. In the first stage of this narrative synthesis, independent reviewers extracted the overarching themes presented by each study in order to identify themes most frequently discussed within the included studies. Any discrepancies in the themes identified by

the two reviewers were resolved through consensus. Using these overarching themes as a framework, sub-themes and more detailed description were subsequently extracted from each study. Relationships between themes were explored. During data extraction, information about the publication such as journal, study design, participant selection, participant inclusion and exclusion criteria, participant characteristics, and findings were also extracted in duplicate from each included study.

18.2.4 Quality Assessment

Included studies were assessed for quality using the Critical Appraisal Skills Programme (CASP) checklist for qualitative literature.¹²⁵ This checklist is comprised of ten questions, each assessing areas of potential bias, such as: was a clear objective was stated, was the recruitment strategy was appropriate, and was data analysis was rigorous.¹²⁵ Each question is answered with “yes,” “no,” or “can’t tell.”¹²⁵ Studies were not excluded based on quality.

18.3 Results

Six-thousand unique citations were retrieved (Figure 17). During abstract review, 59 abstracts were selected by the reviewers and continued to full-text review; the remaining 6,341 were excluded. Five studies were included after full-text review.¹²⁶⁻¹³⁰ Fifty-four studies were excluded; abstract from conference proceedings only (n=31), and not patient perspective and/or qualitative research (n=23). The term patient was defined broadly to include family or close friends, although only one study¹²⁶ included family or friends in the interviews.

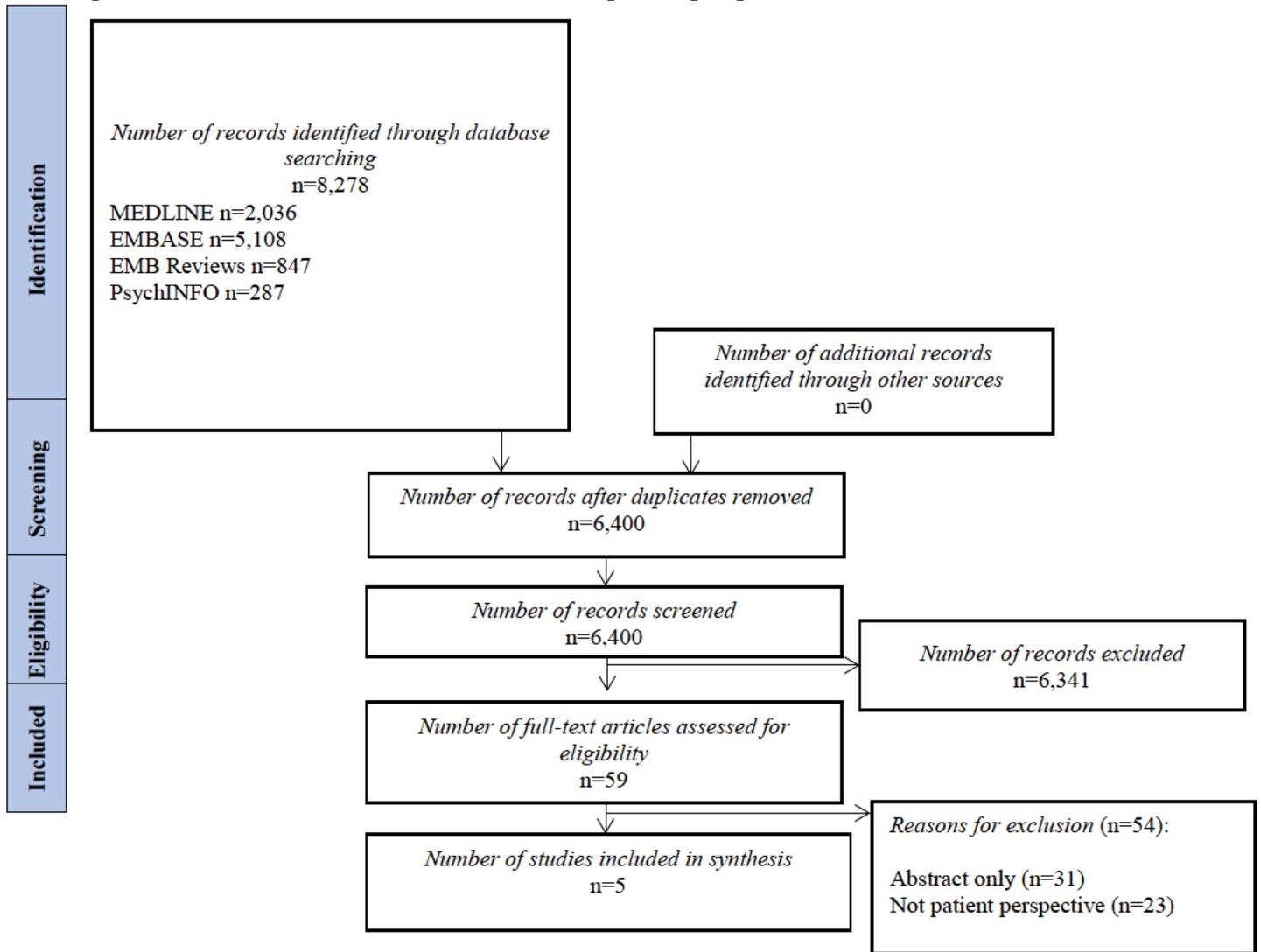
Two of the included studies were from Canada,^{126,128} two from the United Kingdom,^{129,130} and one from Norway.¹²⁷ They were published between 2009¹²⁸ and 2016.¹²⁶ All used semi-structured interviews as a strategy for exploring patient perspective. Each study included between 6¹²⁸ and 20¹²⁶ patients, with a total of 53 patients included across the five studies. Three of the five included studies explored patient experience with SCS chronic neuropathic pain (non-cancer), and together include in-depth interviews with 27 patients.^{127,129,130} One study, also looking at SCS, explored patient perspectives of neuropathic pain, and ethical issues surrounding the original structural surgeon also implementing SCS therapy for treating the pain¹²⁶; 20 patients were interviewed.¹²⁶ The final study explored patient experience with an intrathecal pump for cancer pain and include multiple interviews with 6 patients.¹²⁸ There were no studies

that looked at other kinds of neuromodulation (i.e., transcutaneous supraorbital nerve stimulation for non-cancer pain; peripheral nerve or nerve field stimulation for non-cancer pain).

A number of study authors acknowledged the lack of qualitative research on and in-depth analysis of the neuromodulation journey as experienced by patients,¹³⁰ citing this as an important rationale for their qualitative research. Types of qualitative data analysis used include: Graneheim and Lundmans qualitative content analysis¹²⁷; thematic analysis supported by QSR NVIVO 8.0 software¹²⁹; interpretive phenomenological analysis¹³⁰; and thematic analysis using open and axial coding.¹²⁶

Three studies recruited patients through hospital neurosurgery clinics,^{126,127,130} one through a hospital palliative care unit,¹²⁸ and one through a hospital pain management department¹²⁹; with two using a consecutive patient sampling strategy,^{126,128} one a convenience sample,¹²⁹ one a purposive sampling strategy,¹³⁰ and one did not specify.¹²⁷ In the study by Sparkes et al., two of the 13 interview participants had experience with a SCS trial, but did not proceed to permanent implant.¹²⁹ In the study by Samuel et al., all 20 patients were referred for SCS, but none had experienced with a trial or permanent implant.¹²⁶ There was an equal distribution of male and female interview participants across studies, and these individuals ranged in age from 22 to 70.

Figure 17. Flow Chart of included and excluded patient perspective studies



18.3.1 Quality Assessment

Broadly, the studies were of high quality. The objectives of studies were clear; the methodology, research design, data collection and recruitment strategies were appropriate; and all considered ethical issues. The areas where quality was most unclear, based on the CASP checklist, were related to Questions 6, 8 and 9 on the checklist. Question 6, asks “Has the relationship between researcher and participants been adequately considered?¹²⁵” with a focus on researcher bias influencing results (Figure 18). Only two of the included studies reported any information on the relationship between researcher and participant, the remaining 3 studies were unclear. Question 8, which asked “Was the data analysis sufficiently rigorous” was poorly reported in one study. One study received a “no” for Question 9 which asks “is there a clear statement of findings?”

Figure 18. Quality Assessment of Included Studies using Critical Appraisal Skills Program (CASP) Checklist

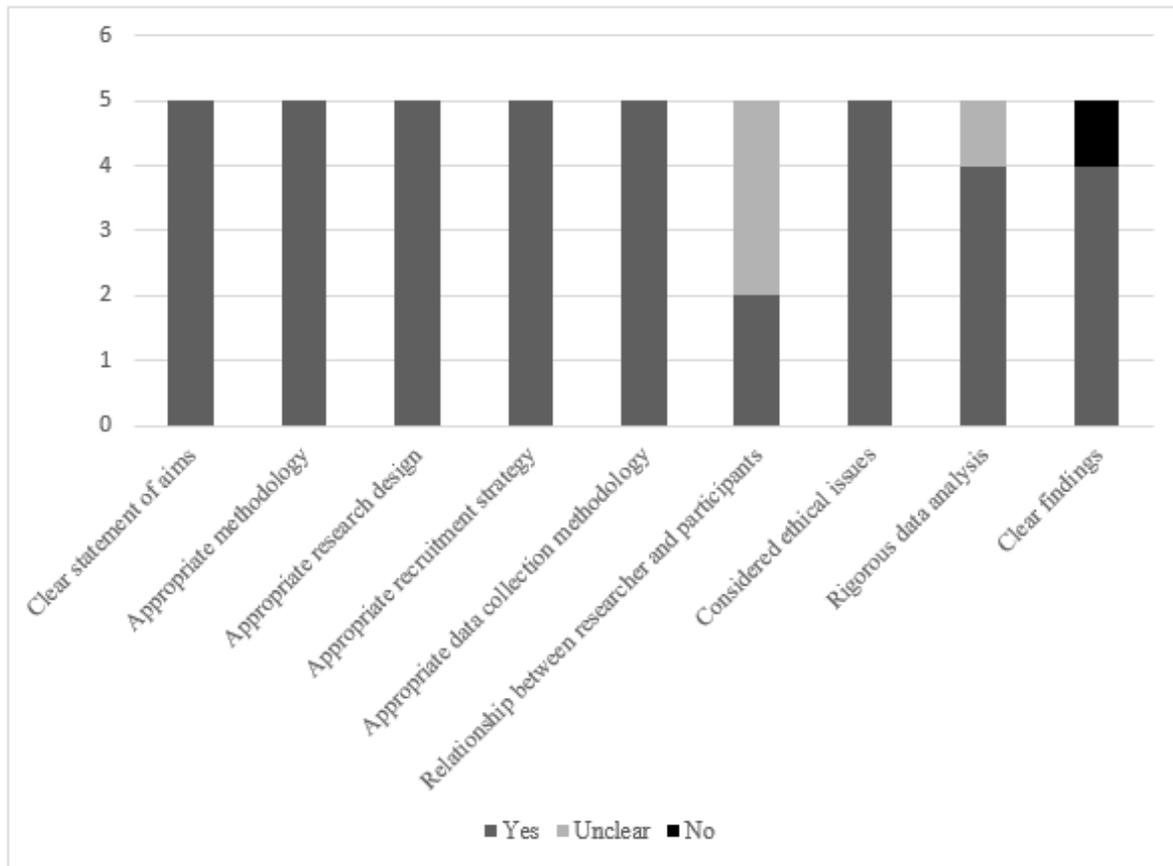


Table 25. Characteristics of Included Patient Perspective Studies

Author, Year of Publication, Country	Study Design	Participant Selection	Participant Inclusion Criteria	Participants Exclusion Criteria	Participant Characteristics	Findings
Gjesdal et al., ¹²⁷ 2014, Norway	Semi-structured interviews, conducted by phone. Data were analyzed using Graneheim and Lundmans qualitative content analysis	Eligible participants recruited through neurosurgery unit in a university hospital in Norway.	<ul style="list-style-type: none"> Chronic neuropathic back pain Nonmalignant pain, implanted spinal cord stimulator Use of stimulator for at least 6 months Age 30-65 Ability to speak and write Norwegian 	<ul style="list-style-type: none"> None listed 	7 patients included: 43% female, 4/7 employed, mean age: 48 (age range: 38-64)	This study identified the following themes: 1) pain relief with spinal cord stimulation as a complex and individual experience 2) challenges in adaptations in everyday life with spinal cord stimulation
Sparkes et al., ¹²⁹ 2011, United Kingdom	Semi-Structured interviews, ranging from 45-60 minutes long. Topics included: pain description and experience, pain history, medication use, pain behaviours, spinal cord stimulation, patients' concept of pain and treatment. Data were analyzed using thematic analysis using QSR NVIVO 8.0 software. Patients were also asked to rate their pain using a	Convenience sample recruited between November 2009 and April 2010 at the Russells Hall Hospital, Pain Management Department. Recruitment stopped when saturation reached.	<ul style="list-style-type: none"> Undergone trial on spinal cord stimulation for 1 year Adults 18 years and older 	<ul style="list-style-type: none"> Refusal to participate 	13 patients included: 54% female, mean age 45.6 (range 32-70), 2 failed trials and did not proceed to full implantation of spinal cord stimulation	This study identified the following themes: 1) coping with pain (helplessness, frustration and anger, responsibility for pain relief, and acceptance) and 2) treatment with spinal cord stimulation (information provision, regaining control, and unexpected experiences).

	visual analogue scale.					
Turner et al., ¹³⁰ 2012, United Kingdom	Semi-structured interviews, conducted in person, ranging in length from 43-96 minutes. Data were analyzed using interpretive phenomenological analysis.	Purposive sample from a neurosurgery department.	<ul style="list-style-type: none"> • Spinal cord stimulation to treat chronic neuropathic pain following failure of alternative treatment to provide relief • Under SCS implantation 2-8 months prior • 18 years or older • English speaking • Consented to participation 	<ul style="list-style-type: none"> • None listed 	7 patients included: 57% female, age range 43-68, all white British; experienced back or leg pain for 6-21 years; all had chosen SCS after failure of other pain treatments	This study identified the following themes: diminished control and coping, identity transitions, and spinal cord stimulation conflict
Hawley et al., ¹²⁸ 2009 Canada	Semi-structured interviews (up to 3 per patient), conducted by research nurse or nurse assistant not involved in patient care. Topics explored included: patient experience, quality of life, hope/expectation, effectiveness, & comfort level with the device. Data were analyzed as stand-alone cases and then cross-referenced with other patients to identify themes.	Consecutive patients receiving an intrathecal pump in a palliative care setting in Vancouver, BC.	<ul style="list-style-type: none"> • Palliative care unit patients with an implanted intrathecal pump or dome catheter for medium or long term relief of intractable cancer pain • Tried multiple opioids by oral and parental routes and adjuvant analgesics as appropriate 	<ul style="list-style-type: none"> • Patients near the end of life who received intrathecal or epidural infusions through a temporary percutaneous catheter 	6 patients included: 50% female, mean age 50.16 (range 22-67), Survival after implant ranged from 11 weeks to 12 months, 4 at home, and 2 were at a residential hospice	This study identified the following themes: coping with the disease (pain prior to implant was devastating and impacted all aspects of their life), quality of life (grief and loss, support); hope/expectation (hope for a life without pain, independence and a sense of control); effectiveness (all patients said implant was helpful, some dramatically so); comfort level with the device (patients were comfortable with it, but anxious about possible device failure)
Samuel et al., ¹²⁶ 2016 Canada	Semi-structured, open-ended face-to-face interviews conducted by	Consecutive patients recruited through	<ul style="list-style-type: none"> • Previously underwent spine surgery and were 	<ul style="list-style-type: none"> • None listed 	20 patients included: 45% female, mean	This study identified the following themes: the importance of pre-operative communication

	<p>one interviewer with patients, and with family members or friends in some cases. Themes explored include: perspectives of PPNP; ethical issues surrounding the original structural surgeon also implementing SCS therapy for treating the PPNP. Data were analyzed by tabulating responses, and using open and axial coding for thematic analysis.</p>	<p>neurosurgery clinics at TW hospital. Recruitment stopped when data saturation reached</p>	<p>referred by a physician for persistent post-op neuropathic pain (PPNP)</p> <ul style="list-style-type: none"> • >18 years of age • Able to speak and understand English • No cognitive deficits 		<p>age 58 years, 14/20 not actively employed, Median time between last spine surgery and interview: 3 years</p>	<p>in calibrating expectations; patient's perceptions of their PPNP as a failure of their spine surgeon; their willingness to have that surgeon either re-operate or implant a SCS; the influence of a trusting patient-physician relationship; the ethical issues of having the spine surgeon who had done prior structural surgery also do the SCS implantation.</p>
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18.3.2 Thematic Analysis

Three themes emerged from four of the five included studies¹²⁷⁻¹³⁰: (1) the individuality and complexity of the experience of living and coping with pain, (2) adapting to and using neuromodulation, and (3) the positive impacts of neuromodulation with respect to both pain reduction and improving function and quality of life. A fourth theme emerging from the fifth study: the importance of the patient-surgeon relationship as an influencing factor in a patient's comfort level SCS implant.¹²⁶

18.3.2.1 Living with Chronic Pain

The patients included in the three SCS studies^{127,129,130} had experienced years of living with chronic pain before considering SCS. The often intense emotions induced by living with chronic pain, include frustration, anger, sadness and fear. This combined with the lack of a distinct diagnosis, and an often “harrowing journey” through the healthcare system can leave people feeling helpless and uncertain of the future^{129,130}; and affects how people are able to cope and continue with daily life.

The majority of patients across the three SCS studies describe struggling with feelings of hopelessness, sadness, low mood, and/or lack of motivation throughout their pre-SCS pain journey.^{127,129,130} These patients also described activity limitations, participation restrictions, multiple losses and dependence as a result of their pain; with much of this due to physical restrictions due to pain. Some also described the side effects of pain medications as contributing to these restrictions.¹²⁹ Turner describes the identity transitions people living with pain experience; with the loss of meaningful aspects of their lives, including significant roles, fragment their sense of self and negatively affecting their self-esteem and mood.¹³⁰

“I used to be part of a walking club, we used to do hill walking, I don't see any of them anymore, because I don't go walking.” (Turner, page 49)¹³⁰

Another emerging theme is something that Turner refers to as the unwanted pain identity.¹³⁰ *“The ‘pain identity’ included both personal characteristics of what participants are like when in pain and how they manage pain socially” (Turner, p50).¹³⁰* The anger described by some of the patients in the study by Sparkes et al. could be an aspect of this pain identity.¹²⁹

‘I get aggressive a lot...it isn’t me, this person from the last 10 years isn’t me....you don’t want to be like that, you don’t want to, you don’t want to treat other people like because you know there are trying to help you but you just want to be left alone, you just want to be (hesitates), packed away into your own life’.
(Turner, page 50)¹³⁰

Patients often described feeling helpless or powerless, because their pain dictated what they could and could not do,^{129,130} and also because of their interactions with the healthcare system.¹³⁰ Medication use was an aspect of pain management that often influenced this sense that their life was being controlled by their pain.¹²⁹

“You can’t live a normal life when you are constantly in pain because your whole life revolves around taking the next pain killer.” (Sparkes, page 243)¹²⁹

People living with cancer pain also described this pain affecting all aspects of their life and being overpowering in its magnitude.¹²⁸

“What’s life living in pain? There’s no meaning; like you just drag yourself and eating all these pills, everywhere you go you feel pain. There’s no life.” (Hawley, page 373)¹²⁸

18.3.2.2 Obtaining and Living with a Neuromodulator

Given the impact that living with chronic pain or intractable cancer pain has on people’s lives, and that neuromodulation is often a last line treatment, people have high expectations for pain relief, independence, and an improved sense of control.¹²⁸⁻¹³⁰

“Hopefully that what it is going to enable me to do is to carry on more of a regular life.” (Hawley, page 374)¹²⁸

In addition, some patients describing having to fight to get the treatment and felt desperate by the time they were offered the SCS, which made trying to keep their expectations for SCS reasonable a challenge.¹³⁰ Sometimes the processes in place to select good candidates can contribute to a feeling of powerlessness, and a lack agency in patients hoping for neuromodulation. For example, one patient was refused a SCS replacement as she had not experienced a 50% reduction in pain and wondered why her subjective experience of how her SCS improved her life was not valued.

“[She] was unable to comprehend this disparity in opinions about what constituted ‘adequate pain relief’ leaving her feeling devoid of agency.” (Turner, page 47)¹³⁰

In the same study, another patient was described as struggling to hide her emotions from healthcare professionals so she would not be denied a SCS replacement.

“In her desperation for pain relief, she feared being denied SCS for exhibiting low mood and distress, so began concealing her emotions from healthcare professionals. She described feeling emotionally unsupported during this process, leaving her feeling angry: I should have been able to be emotional, I should have been able to talk to someone that helped me be ok for the spinal cord stimulator, and help me be ok if it didn’t work.” (Turner, page 48)¹³⁰

Patients identified the importance of having access to information about the device they were to have implanted, how it worked as a pain management tool, and what it was like to live with an implant, before they participated in a trial.^{127,129,130} Patients in two of the SCS studies specifically said that they would have appreciated having an opportunity to speak with patients who had a SCS.^{129,130} People who expressed more satisfaction with their knowledge about SCS had done their own research on the internet.¹²⁹ The limitations of SCS should be clearly explained to patients as part of the pre-trial patient education, so patients are able to make a fully informed choice about whether they want to have a SCS implanted.¹²⁷

Related to this need for good information before proceeding with a trial, is the unexpected experiences related to SCS described by patients including the SCS trial itself (i.e., the surgical procedure)¹²⁹ and body image concerns.^{127,129,130}

“Whilst actually in hospital having it done, I did get the feeling that some of the nurses didn’t quite understand the severity of the operation that we’d had” (Sparkes, page 246)¹²⁹

“. . . the only shock I had was the size of the scars. I wasn’t expecting that.” (Sparkes, page 247)¹²⁹

“It [the battery] does stick out, whereas, I, my idea of an implant was it would go in and you wouldn’t notice it.” (Turner, page 131)¹³⁰

“I had a foreign element implanted—what was I? A robot?” (Gjesdal, page 16)¹²⁷

Once people had their device implanted, they frequently experienced some adaptation in their now new life with a SCS.^{127,129,130} Turner described this phase as disappointment, adaptation, and acceptance. Acceptance of living with pain often came from the realization that although the pain may not be able to be completely beaten, it could be managed as a normal part of their lives.^{129,130}

“Participants were experiencing a process of acceptance of their level of pain relief and capabilities. This process could be the start of the end of their battle. Having tried most, if not all treatment options, it represented an opportunity to stop trying and accept life as it is.” (Turner, page 53)¹³⁰

Some patients felt disappointment when their expectations were not fully met; with a major reason for this being that some patients had expected that the device would completely get rid of their pain.

“The impression was that it would totally get rid of the pain...um...which it hasn’t done, but then I don’t know whether that was expecting too much or whether the doctors expected it to get rid of the pain entirely.” (Hawley, p 373)¹²⁸

Sparkes found that acceptance was more likely when patients got at least 30% relief of their pain through SCS. Emotional coping was described as still important, even when pain is being more effectively managed.¹²⁹

Although most patients described being able to participate more fully in everything activities with an SCS, there were some examples also of the SCS hampering participation. These included the inability to do some physical activities where there was a risk of falling (e.g., skiing, skating); unpredictability of some of the SCS’s varying effects (e.g., electric shocks, variable effectiveness); and worry related to the impact of the SCS on other electronic equipment.¹²⁷

Some patients experienced some negative side effects or complications with the SCS, with the most common ones described including: electronic shock feelings; incorrect stimulation due to problems with the electrode placement; and lead or battery revision.

“You know that it’s electric, and I still receive shocks depending on the way I move.” Gjesdal, page 16)¹²⁷

“When I use the stimulator, I feel the stimulation in the esophagus, and after a while I feel like I have to throw up.” (Gjesdal, page 16)¹²⁷

With respect to cancer patients experience with the intrathecal pump, Hawley found that patients were generally comfortable with the pump but had anxiety about the possibility of device failure. This was an issue in part because considerable expertise is required to handle these pumps.

“If I have an emergency outside my home jurisdiction which is Vancouver...how...sometimes I wonder if I would get easy access to somebody who understands the intrathecal pump.” (Hawley, page 374)¹²⁸

18.3.2.3 Positive impacts

All patients who proceeded past the trial stage to have a SCS or an intrathecal pump implanted described some positive impacts, including: pain relief; better able to cope with and/or manage their pain; feeling more positive; feeling more independent; and being able to do more in their lives. Some patients experienced dramatically positive impacts.¹²⁷⁻¹³⁰ Yet, as Gjesdal noted, pain relief is a complex and individual experience.¹²⁷

The patients with cancer pain all found the pump implant to be helpful, and some experienced a dramatic improvement in their pain.¹²⁸

“Without intrathecal, quite frankly my pain would be so severe; I would be around 9 all the time... and now 5 is the average and it goes down to 2, and in this position sitting I feel like it is 0...yeah...it’s unbelievable. So this having the pump has saved me a lot of trouble, from trouble from terrible nights.” (Hawley, page 374)¹²⁸

Almost all of patients with SCS also experienced some relief in their pain, and again some dramatically so.^{127,129,130}

“It’s getting on for eight years now from when it [the pain] all started, so you’re talking about, six months ago, so seven and a half years with not been out of pain, to the pain being reduced by something like 90%.” (Turner, page 128)¹³⁰

“It’s [SCS] probably the best thing that’s happened...I suppose in the long run, it’s probably saved my life...it’s given me the chance to start looking forward” (Turner, page 51)¹³⁰

The many patients who had obtained some pain relief as a result of their SCS described being better able to manage and cope with their pain, so feeling they had more control over their pain rather than having the pain have control over their lives.^{127,129,130}

“The help that I have from the stimulator allows me to deal with the pain in a different way—to better cope with it.” (Gjesdal, page 16)¹²⁷

“...now that I’ve got the implant, I can cope with the pain more. It’s not as severe when the machines running. I look forward to the day to begin. Whereas before I didn’t want to wake up in the morning because I knew I’d get the same thing to look forward to everyday. I know it’s still there now, and it’s, it’s not nice but I know I can go and do something about it when it gets bad. I can go shut myself away in the room, put the machine on and the helps there.” (Sparkes, page 246)¹²⁹

They were also able to reduce or completely stop using medications, meaning that they were able to avoid the side effects of the medications. This contributed to feeling more in control over their pain and enabled them to function and participate more in life.^{127,129,130}

“The very best thing is not having to deal with the side effects of medications.” (Gjesdal, page 15)¹²⁷

“It is just unbelievable having such a function instead of being drugged by medication.” (Gjesdal, page 16)¹²⁷

One of the strongest themes across these studies was patients describing their lives as improving, in that they felt they wanted to and were able to do more in their life.¹²⁷⁻¹³⁰ Their social function improved, and they were able to participate more in everyday activities.¹²⁷

“Pain brings limitations, and when the pain disappears, you have the opportunity to participate more in everyday life.” (Gjesdal, page 16)¹²⁷

“I may experience pain relief for 3 or 4 hours, and then it goes without saying, that you have a stronger desire to do stuff.” (Gjesdal, page 16)¹²⁷

Some patients described this as having more independence.¹²⁹

“. . . I think it's given me a little more independence back, because I do go out walking every day, umm and I think that's where I have lost the weight. Umm so I think yeah from that side, you know, it's given me independence, you know.”
(Sparkes, page 246)¹²⁹

Finally, many patients reported feeling more positive, likely due to both having some reduction in their pain and being able to do more in their lives. Turner noted that: “It seemed the positive effects of the stimulator disrupted feelings of persistent low mood, lack of successful pain relief and hopelessness.”¹³⁰

18.3.2.4 Patient-Surgeon Relationship

One study had a specific focus which was to explore with patients a specific issue: their views about their persistent post-op neuropathic pain (PNNP), and about any ethical issues surrounding the original structural surgeon also implementing SCS therapy.¹²⁶ This study found that patients' perceptions of their PNNP was influenced by pre-operative communication, in that it shaped patient expectations, and their view on whether their pain was due to a failure of the surgeon or the surgery.¹²⁶

Although more than half of these patients indicated that their previous spinal surgery had not met their expectations, 75% of patients did not feel that their current PNNP was due to failure of the surgeon. The main reason for this was effective pre-operative communication between the patient and the surgeon.

“No, I was told before the operation that there is nerve damage. Was I given an accurate prognosis? Yes I was. Was I given guarantees? No I wasn’t.” (Samuel, page 276)¹²⁶

An important finding was that many of these patients, would not want this surgeon to do any further surgery on them, including implanting a SCS. The primary reason given by these patients was the erosion of the patient-surgeon relationship. This breakdown in the relationship, was described as being related to a lack of accountability post-op, as well as an absence of appropriate follow-up.¹²⁶ Therefore, although they did not blame the surgeon for the failed surgery, patients did hold them responsible for the ongoing care that they did or did not provide.

“From the sounds of it, he did his job. You can’t always blame everything on the surgeon. What I wasn’t happy about was his lack of follow-up. He just said that his job was done and he was done with me. Had he followed-up on everything, I would’ve been okay with it [having him perform another operation].” (Samuel, page 276)¹²⁶

Patients were asked whether they perceived any ethical issues related to having the spine surgeon who had done prior structural surgery also do the SCS implantation; with the majority saying that they could not see any ethical problems with this scenario. The more important issue was felt to be whether the patient had trust and confidence in the surgeon’s competence.¹²⁶

“It would come down to the reason. If he failed because he was given something complicated and 9/10 doctors would’ve failed anyway, it’s different than if he failed because he was incompetent” (Samuel, page 276)¹²⁶

“There are good surgeons that can’t fix people.” (Samuel, page 276)¹²⁶

As long as patients believed that their PPNP was not due to a surgical complication or physician negligence, they were more likely to accept this diagnosis and willing to work with their health

care team to find the most appropriate treatment to help decrease their pain and to improve their quality of life.¹²⁶

Finally, moving toward the use of the PPNP rather than FBSS is supported by this research, as the latter term reinforces failure of the surgery rather a condition – PPNP – which sometimes can be helped by structural spine surgeon and sometimes not. Note that this study only included patients who were in debilitating pain and unable to work.

18.4 Conclusion

These five studies¹²⁶⁻¹³⁰ paint a picture of the experience of living with pain, making the decision to try a neuromodulation device, living with the device, and the difference these devices can make in people's lives. Pain relief is a complex and individual experience. Some patients experience a dramatic and immediately life-altering reduction in their pain, but for many patients the pain relief was less dramatic yet they still experienced considerable improvement in their quality of life.

Patients have often experienced a long and harrowing journey, both with their pain and with trying to find some effective treatment and support, before they consider a neuromodulation device as a treatment option; it is important to consider the experience of neuromodulation in the context of the journey that preceded it. Both SCS and the intrathecal pump are considered to be last-line treatment options for people living with chronic pain.

In one study,¹³⁰ two patients experienced considerable difficulties in accessing a SCS. Turner et al. noted that there is a dearth of literature on patients' experiences in obtaining a SCS, so this is an area where more qualitative research would be beneficial. Certainly, initial insights from her study indicate that emotional support may be helpful during this process. If complications arise, such as a patient being turned down as a result of an unsatisfactory trial, the consequent powerlessness and associated anxiety might further exacerbate their pain experience.¹³⁰ Hawley et al. also noted that pre-pump implant psychosocial assessment, for people living with devastating cancer pain, can be extremely difficult. Again, the importance of multi-disciplinary team support was stressed.¹²⁸

Patients need to have access to accurate information about the device, how it works, and how it may help them manage their pain before a trial is even considered. In addition to having pre-trial education sessions with health care professionals, many patients with SCS's talked about how valuable it would be to be able to speak to another patient living with a SCS before they participated in the trial. This would help prepare them for the trial, as well as what it was like to live with an implant, and the adaptation required.^{129,130} There can be fear of device failure, and this is a particularly important issue with intrathecal pumps. Hawley et al. stresses the necessity of a close liaison with care providers in the patient's home community, and access to on-call anesthesia, to reduce patient anxiety.¹²⁸

The importance of presenting accurate information about the likely benefits of an implant was stressed across all studies; that is, it needs to be clearly communicated that a SCS or an intrathecal pump will reduce pain and enable you to do more but it will not fix your pain or make it disappear entirely. The findings in these studies support what has been found in other research, which is that improved functional status is the most important benefit for patients. Being able to do more, to participate more fully in life, was described by patients as being far more important than a certain % change in pain relief. And with SCS, this ability to do more is related to patients feeling they have more control over their pain, they are in charge of managing their pain with the SCS; they feel less helpless and powerless.

Finally, many of the study authors concluded, based on what they had learned from the patients they interviewed, that SCS is often not effective on its own but should be part of an overall pain management plan that may include the need for ongoing emotional and psychosocial support. Learning to live with and optimize the potential benefits from a neuromodulation device, and in particularly SCS, takes time and requires some adaptation and support from a multi-disciplinary team. Clearly, the development of trusting relationships between patients and healthcare professionals is a critical component of such a biopsychosocial approach.

19 Key Informant Interviews: Patients

Summary

- Eleven patients and two family members participated in in-depth telephone interviews
- Eight of the patients live with spinal cord stimulators (SCS) and two with intrathecal pumps. One patient experienced a failed trial with a SCS so is not currently living with a neuromodulation device.
- These patients described trying many treatments and strategies to manage their pain, often over a period of many years, before becoming aware of neuromodulation as an option
- Their experiences navigating through healthcare services to find their way to a pain clinic that could provide neuromodulation as an option was often challenging
- The way people were treated at the pain clinic, including being listened to, believed, and treated with dignity, respect, and compassion, was described as very important
- For these patients, neuromodulation has made a huge positive difference to their quality of life; with most saying they are not sure they would still be here without it
- All patients described having far less pain, being better able to manage their pain, and using far less other healthcare services

19.1 Purpose

To understand the patient experience of obtaining and living with a neuromodulation device to help them better manage and live with chronic pain, and to solicit their views and insights on neuromodulation as a pain management tool and where it fits as part of an overall pain strategy for BC.

19.2 Methods

Telephone interviews were conducted with patients who had experience with using neuromodulation for pain. Patients were recruited using three mechanisms: Patient Voices Network advertised the opportunity to their patient partners; Pain BC advertised the opportunity through their newsletter and social media platforms; and, the St. Paul's Hospital and Nanaimo General Hospital's pain programs handed out invitations to their patients, asking them to contact the HTA Unit at the University of Calgary directly if they were interested. An effort was made to speak with individuals from across the province and who had experience with both spinal cord stimulators and intrathecal pumps.

A semi-structured interview guide was developed to support the interview process. This guide included questions on: the pain programs, current patterns of neuromodulation practice, perceived benefits and challenges, and insights into the future of neuromodulation in BC. The guide evolved over the course of the interviews, as questions were refined to reflect what had been learned through the previous interview(s). All interviews were conducted by an experienced

qualitative researcher, audiotaped with the consent of the interview participants, and detailed notes were taken. The data were qualitatively analyzed using constant comparative analysis to identify key themes.

19.3 Findings

19.3.1 Participants

Twelve telephone interviews were conducted with 13 people from May to July 2018, 11 patients and two family members. One patient was interviewed with their spouse. The interviews ranged in length from 40 to 75 minutes. Eight of the eleven patients were living with spinal cord stimulators (SCS), and two with intrathecal pumps, for a variety of pain conditions including: complex regional pain syndrome; post-trauma abdominal pain; back pain; and neuropathic back pain. One patient experienced a failed trial with a SCS so is not currently living with a neuromodulation device.

The date of initial implant ranged from 1991 to 2016, with six of the eleven patients having lived with their devices for more than a decade. Six of the patients were women, and five were men, and they live in cities and towns situated in four of the five health authority jurisdictions: Vancouver Island (n=4), Vancouver Coastal (n=1), Fraser Valley (n=3) and Interior Health (n=2). One patient interviewed currently lives in outside BC. Seven of the 10 patients living in BC were currently being followed by the St. Paul's Hospital pain program (Vancouver Coastal Health Authority), and three by the Nanaimo General Hospital's pain program (Vancouver Island Health Authority). A number of them also had experience with other pain clinics in BC and in other provinces; three of them had their original spinal cord stimulators or intrathecal pumps implanted in other provinces and had subsequently moved to BC.

19.3.2 Living with pain and the kinds of pain management strategies tried prior to considering neuromodulation

All the interview participants described experiencing an acute injury, or in one case a series of injuries, that led to the development of severe chronic pain that had a substantial negative impact on their quality of life. They described trying a number of different treatments and strategies to manage their pain, often over a period of many years, before becoming aware of neuromodulation as a potential option. These included a variety of medications (e.g., anti-seizure drugs; opioids; anti-inflammatories); interventions (e.g., nerve ablations; facet and paravertebral

nerve blocks; prolotherapy); and other pain management strategies (e.g., acupuncture, chiropractic, massage therapy, TENS). Some patients had undergone numerous surgeries.

Most of these patients described the side-effects of the medications and particularly the opioids or narcotics they had been taking, pre-neuromodulation, negatively. People described these oral medications as not working at all for them, as they made them feel tired, and “out-of-it”, and sick. Many said they could not live their lives, including doing their job, while taking these drugs. In addition to these side-effects, for many people the costs of these medications and of other treatments not covered by BC Health or insurance created hardship. One patient stated that he spent over \$10,000 on medications and other treatments in the few years before his implant; in the first year post-implant he had spent less than \$2,000 and expected this to continue to decrease.

19.3.3 Learning about neuromodulation as an option, and the assessment and trial process

These interview participants lived in pain for between 2 and 18 years before learning of neuromodulation as an option, with a number of people living ten years or more in severe pain before receiving their implant. Many described this period of their lives as being “horrible”, with many specifically talking about how hard this had been on their families. Some spoke about experiencing severe depression. Many people said they did not think they would still be alive if they had not found their way to a good pain clinic and neuromodulation.

“I can distinctly remember I took a walk---I walked my dog and there was a time when it was so bad that I was afraid that I couldn’t continue on living with it, but yet I was afraid that if I tried to say for instance to commit suicide, would I be forever living in that afterlife with the pain? It was that bad.”

“I can’t say too much about it you know because that pain is so overwhelming and it takes over your life so much and particularly the first five, six, seven years when it was so bad. And again, I was on so many narcotics. I was kind of crazy and without that machine I don’t know if I’d have a life. And I don’t want to sound too over dramatic, but that’s the truth. I feel I owe my life to that machine. And although because of my injuries I haven’t been able to work you know. I’ve been able to enjoy my family.”

“They would admit me to the hospital and give me epidurals. But...basically like nothing was working and my pain was really bad. I was on methadone for the pain... and it was just horrible. Like I was suicidal because it was so bad.”

Family members also described how difficult the period of time pre-implant was for them and the people they love.

“You know as a family member to sit and watch your loved one and the most important person in my life... watch [them] suffer and not be able to help is a very difficult thing to witness and be part of.”

For many the journey through the healthcare system, trying to find someone who could help them, was convoluted and long. A number of patients described ending up in the emergency room (ER) with severe break-through pain, as they had nowhere else to go.

“So despite the fact that the medical system washed their hands of me, the pain continued and it was...the best that I can describe it, I just sort of lurched my way through the medical system, trying to figure out what to do. And would wind up going into the local Emergency Room and sometimes two or three or four times a year to sort out break-through pain and it would just go out of control... and they would treat me either for a day or sometimes they'd work for two days until we got things back under control and then out you go again. So in amongst all of that and trying to string together some sort of normal life, I kept trying to reach somebody who could help me.”

Most people described being offered neuromodulation as a final option, after they felt they had literally tried everything else.

“...there wasn't really any other option. You know it was a shot in the dark because I was becoming so incredibly unable to function due to the pain.”

Getting a referral to a multi-disciplinary pain clinic that offers neuromodulation as an option was a life-changing moment. Many of these patients had been living in severe pain for a number of years before a referral to be made, and then spent more time waiting for an initial appointment. One patient said s/he waited more than two years to get an appointment, once the referral had been made. The experience of going to such a pain clinic, being listened to, having someone

believe they were living with considerable pain and trying to figure out what might help them, and overall being treated with kindness, dignity and respect, was described as a positive experience for many people. This difference in how they were treated is what seemed to stand out and was the first thing many people described.

“I remember [the initial intake] very clearly because this was like up to a dozen times I had related my history to a doctor. I’m going through it by rote and I’m just like I’m wasting my time and here we go again. And then I realized that he kind of stopped talking, and I looked at him and he put his pen down and he said, you know these words that will resonate with me for the rest of my life. He said it’s okay, because we believe you. And up until that point in my life I had never had anybody say that they believed me. I always felt like I was being looked at sort of with that side eye and really what’s wrong with you? So my first recollection of the history and the initial intake was I had met a group who demonstrated compassion and understanding and truly understood that this was real and it wasn’t something I was making up.”

With respect to the rest of the assessment and trial process, it was described as rigorous and thorough. Some patients described it as being a little uncomfortable, and in particular meeting with the psychologist, in part because they were not used to exploring the mind-body connection and they were afraid they might be assessed as not eligible. One patient described it as very time consuming, and particularly difficult to attend all the different appointments and classes while trying to continue working. Yet others described it as hard, in part because they were still experiencing a lot of pain.

“When they wanted to start talking about my mind, I was quite concerned about that because again I was thinking maybe I am crazy or making this up and then what’s going to happen?”

“I was in such a state of pain that I just didn’t want to live. There was no emotion back then about it. It was just another talking to people and telling my story and talking about my pain and how bad it is and that sort of stuff. So yeah, it was a little bit of a kind of like another hoop to jump through.”

Many spoke about their understanding of why it needed to be so thorough, as follows: the patient needs to be able to understand how the device works and to learn how to use it; they need to have the “right temperament” to be able to benefit from the device; and due to the cost of the devices they need to ensure that they are going to those patients who are likely to benefit most.

Once the assessment had been completed, and patients were informed that they were eligible for either an intrathecal pump or a spinal cord stimulator, they were told approximately how long they would have to wait for the trial and then the permanent implant should the trial be successful. Some of these patients ended up getting their trial far sooner than they had expected, as someone else had cancelled, for which they were very appreciative. One such patient described how valuable she found it to be able to speak with a patient living with a spinal cord stimulator immediately before her trial, particularly given it was happening so quickly.

“It was actually really nice because the Monday morning when I was in there they actually had a patient in there that had one. And so they allowed me to talk to him...both my [spouse] and I were in a state of anxiety, do we do this or don’t we? And he was just you know it changed my life. And so, we were like okay, we’re good and let’s go.”

“I think it makes a really big difference because it’s not just a doctor telling you it’s going to work and here’s the percentage and blah, blah, blah. Well, you’re the human being that’s had this done to them and this is the type of success that they achieved.”

A number of patients said they would have found it very helpful to speak with a patient living with a neuromodulation device prior to having their own implanted, with some saying they would be willing to talk to patients about what it is like to live with a device.

Others spoke about having to wait a long time for the trial and the permanent implant, once it had been determined they were eligible, which again they described as difficult when you are living in severe pain.

“And then once I saw him, then it took forever to wait to get the surgery too. So there was a really long wait time, which is like unbearable when you’re in that much pain.”

A few people described having very low expectations going into the trial, in part because they had tried so many different treatment options that had not been successful for them or their

spouse. Many said that they knew as soon as the device was turned on that it was making a big difference to their pain.

“Now, all the literature and everything that they said, you know I could expect up to about a 70% relief in pain. And for me it felt far more than that. The first time I turned on the machine it was kind of sheer ecstasy. The relief it gave me was just unbelievable...I don’t want to sound too over dramatic about this, but that machine---that first machine literally saved my life.”

“But when they did this trial and we saw it, it was just like oh, my goodness, this is phenomenal. This is actually working... the thing is working right away and s/he can feel it. And I could see that there was hope in her and that to me was---it was amazing. It was incredible process to watch it...It wasn’t like oh, this is going to take months and months and months. This was like now, somebody turn a light switch.”

For others it was a little bit more of an evolving realization that something was different, and in part because they were being cautious about getting their hopes up.

“I recall fairly early on in that first week and I’m like hey, something is different. You know at first it’s hard to quantify anyway and part of it is I think I didn’t want to get my hopes up, so I was being very cautious and sort of very deliberate in my own assessments...I didn’t know what to expect. I knew it wasn’t going to quote, fix it. I gave up years ago looking for a fix; I was just looking for something to make it more manageable. And I started to realize that this thing in me is kind of making it a little more manageable. And I think at that point I really tended to start to perk up a little bit. Like hey, wow! Maybe this will really do this.”

19.3.4 Living with a neuromodulation device, and its impact

Living with a spinal cord stimulator or an intrathecal pump was described by these patients as pretty uneventful, in that they were able to easily integrate it into their lives. Most of the time they didn’t think about the device; it was simply in the background, particularly people who had been living with their device for many years. Most patients described having their spinal cord stimulator on all the time, whereas a few noted that they didn’t use it when driving – as that was prohibited. People said that the only things they really had to pay attention to with their spinal

cord stimulator was recharging them every 4 to 14 days, with the frequency depending on how much they were using them and keeping their handheld controller close by so they could adjust their stimulation as needed. Some patients living with spinal cord stimulators appreciated being trusted by health professionals, once they had developed a deeper understanding of the device and how it worked, and being given broader parameters within which they could do some self-programming.

Many described being able to live full and active lives, with some being able to return to or continue working. They spoke about being excited to do things again, to be active and be part of their families. The improvements in mental health, being able to have hope and dreams, and the desire to live again, as a result of not being in severe pain every minute of every day, was described by many as life-changing. For some, simply “being able to be up and about”, to be able to go for walks, made such a big difference in their lives.

“So basically I went from being pretty much unable to do anything where most people today have absolutely no idea of my history and what I had to deal with. I train and ride horses and I work four or five days a week as well at a market convenience store. I garden; I maintain my home. I work at the farm where I have my horse.”

“So my head space from when I first got it to now it’s just like night and day. Like I’m excited for life and the challenges and I’ve learned to pace and help manage, but I’m just excited to do things and be active and be a part of my family and laugh and smile again.”

“[Spouse’s name] was brought back to part of our life. S/he was off the couch; s/he was able to interact with us as a family and do things that until that point she had been marginalized from... Where there had been this dark cloud over us it’s all light.”

Many patients described having large reductions in the amount of pain medication they are taking, with some taking none at all on a daily basis. They also had far less interaction with the healthcare system, with many saying they no longer had to go to the ER with severe pain, had fewer visits to specialists and their family physician, had fewer other kinds of pain interventions and were no longer having surgeries that were “fishing expeditions”. Rather than spending a lot of their time getting and seeking treatment, they were using that time to live their lives.

“Well, pretty much now I just follow up with my primary care physician. And the only time I go see the pain physician is if for some reason I feel there’s a problem that needs to be addressed. Like when my battery needed to be replaced. So very infrequently. It’s really freed me from having to---because before I was constantly having to go to the pain clinic and sometimes once a week and sometimes and then it got to once every other week and then once a month. So now I mean I feel like that leash is not there anymore.”

Although all of these interview participants described the neuromodulation device as life-saving for them, they also stressed that equally important as the device, was the way the people at the pain clinic treated them and what they were taught about pain and management.

“It’s such a group of amazing people. They’re very caring and so genuine in their care, but they also have really just make sure I have my freedom to live my life...I don’t want to be sort of treated as if I have a problem...And they never have done that. They always encourage me to just get out and live life and they’ve done everything to support me to do that.”

Most patients living with spinal cord stimulators described going for annual follow-up appointments at their pain clinics, once their implant was working and their programming optimized to support their pain management. The first year post-implant often involved a number of visits, and then once a year for a check. Patients with intrathecal pumps had to return more frequently, every 3-4 months, to have their pumps refilled. People did have some experience with complications, including lead breakage, leads getting disconnected from the generator and the anchors for the leads tearing. One patient experienced a serious complication where her pump stopped working, and she failed to recognize the symptoms or notice the alarm. None of these deterred these patients from continuing to use their devices, with none of these people being able to imagine living without them.

19.3.5 The best and worst parts of their ‘pain journey’, and living with a neuromodulation device

These patients described the best part of their experiences trying to manage and live with their pain as finding a pain clinic where people listened and were willing to work with you to help you manage your pain; people who care about you; and no longer having to live from one medical appointment to the next.

“The neuromodulation is obviously critical, but again I put that in the file in the biomedical box... Like really I mean I did struggle on and off for years thinking that there was something seriously wrong with me because if this was all in my head why would I be making this up? So that support, belief and understanding is probably the single most important thing that stands out to me.”

Some patients described their pain clinic as a caring community, and the nurse as instrumental in creating this kind of community where the staff provided support but also created a space where the patients could support each other.

“...there was a nurse at the pain clinic who just like always went out of her way for all of the patients...we were like a community at the pain clinic. Like all the patients knew each other and it was like a really caring community there. And that was just amazing... even if I didn't have an appointment, if I was having a really bad pain day, I would show up there and I knew at least like there would be someone there who would understand what I was going through. And like that made such a difference, even just having like someone who understood made such a difference.”

With respect to the worst part, there were a variety of responses. For some patients, it was their initial injury, for others it was not being believed and being told that their “pain was all in their heads”; and for others it was the “I'm sorry I can't help you” over and over again.

“And at one point I had my family GP say to me; there is nothing wrong with you; it's all in your head, so there's nothing more we can do.”

One patient living with severe pain due to complex regional pain syndrome described the lack of continuity as the worst part, as she had so many appointments to manage after her injury. S/he said it would have been so helpful to have someone make sure her appointments were better organized.

“So here I am and immune-compromised, in so much pain...I'm going to the hospital like four or five days a week because all my appointments are on different days...Yeah, so it's just exhausting for people who are already super-ill to have to manage all of these appointments and like not only just like getting to all the appointments, but actually having the energy to make all the phone calls and follow-up and making sure that they've

made the appointment with the specialists and then making sure they have like their travel vouchers to be able to get on the ferry...”

And finally, another patient described how costly it had been for them to manage their pain, before they got a SCS.

“I was self-employed, so I don’t have all these medical plans that most people do. So one time it was ten thousand dollars a year I was spending on drugs and therapy.”

These people did not want to see other patients have to travel a similar lengthy and convoluted path, to have other family members have to witness this kind of sedated suffering for so long.

“I never would want to watch any of my family members suffer. And it’s kind of like you suffer in this sedation. You’re heavily sedated and you’re numb from the world around you and you’re prevented from being able to truly help yourself I think in some ways.... that being said, this journey I wouldn’t wish on anybody. It was heartbreaking and depressing and you know, sad.”

19.3.6 The future of pain treatment and neuromodulation in BC

Accessibility to a good, person-centered comprehensive pain program which provides neuromodulation as an option was described as being most important. These patients wanted future patients to be able to access this option much more quickly than they had been able to; there is a need to speed up the process which involved increasing awareness across healthcare about neuromodulation as an option. Related to this is better continuity of care and more support in navigating what can be a complex array of health care services. Some referred to the ideal future as a hub and spoke kind of model.

“In a perfect world it’s developing a provincial strategy and just being more part of it. But again, this is sort of my bias, so it would be part of this fabric called the Provincial Pain Strategy and a neuromodulation center of excellence...So St. Paul’s role would be to do the major work that they do, so the surgeries would be done. But throughout BC in all these communities people would still have the support...So kind of the hub and spoke and St. Paul’s being the hub and various spokes reaching out throughout BC to be able to support that work.”

They also want to see other tools, and the encouragement to live a full life, be integrated into these multi-disciplinary pain programs that support neuromodulation and to help people live as full a life as possible with pain.

“So I think that yeah, that the pumps are incredible and I certainly would hope that they’re available to make a difference in people’s lives. But as I said, that support and the program or whatever it is to help someone be the very best they can be. Because then I think--I always feel a sense of gratitude that I have it. So when I stop to think about it...I just can’t imagine where my life would be and because you feel like that it compels you to live that full life and make a difference.”

Access to information was also described by many as an important component of any pain program; information about their conditions, about pain, and about different strategies for managing pain. They appreciated the opportunity be engaged in their own care.

“I found like personally that reading, like scientific articles and stuff about my condition was really helpful. So like the patient engagement piece, right, was really helpful for me.”

Finally, some spoke about the ongoing improvements in technology making the future even brighter for neuromodulation. For example, the devices are shrinking in size, making them more comfortable. The rechargeable batteries mean that battery replacements are required less frequently, and the newest SCS’s are MRI compatible. The programming capabilities are becoming increasingly sophisticated, providing more options for patients.

19.4 Conclusion

The experiences described by patients and family members in these interviews resonated strongly with both the findings from the systematic review of the literature on patient experience with neuromodulation, and with the findings from the interviews with BC health professionals. For those patients whom neuromodulation works as an effective pain management strategy, it was described as a life changing experience; with some also describing finding their way to a good pain clinic as equally life-changing. That is, the opportunity to learn more about the origins of pain and a variety of pain management strategies, and perhaps more importantly being treated

with compassion, dignity and respect and be invited to get more engaged in their own pain management in a way that works for them, was noted by many as being critically important.

Many of these patients lived in severe, life-altering pain for many years, a number for more than a decade, before learning that neuromodulation might be an option for them. The process of going through the rigorous assessment process culminating in a trial was described as difficult by some, although most understood the importance of determining a good fit. The most difficult part for many patients was the anxiety surrounding what they would do if it was determined they were not eligible for a device. For those patients who were trying to maintain a job, finding the time to attend all the required appointments and classes could be a challenge.

Living with a neuromodulation device seemed to be uneventful for most patients, in that they were easily able to integrate managing the device into their lives. Most of the complications they experienced were able to be dealt with quickly, and for the most part people described being finally able to get on with their lives. They no longer felt tethered to the health care system, not having to go to attend multiple appointments to obtain pain relief interventions, medication prescriptions, and or seeking other kinds of help. The most life-altering aspect of neuromodulation described by many of these patients and their family members was the ability to decrease or stop the amount of opioids they were taking. These medications had often prevented them from participating in life the way they wanted to.

Like the healthcare professionals interviewed, these patients feel strongly that neuromodulation is an important option to make available for the subgroup of patients living with severe, life-changing pain who are likely to benefit. They would like to see more awareness of neuromodulation as an option, and a less arduous journey to neuromodulation in the context of a multi-disciplinary person-centered pain program, for other patients in the future.

20 Emerging Applications of Neuromodulation

Neuromodulation has its roots in accidental electrical stimulation.²⁸ However, there has been much progress. Devices have now been developed to last longer and take up less space, rechargeable batteries can now last up to 25 years and implantable generators are smaller than a hockey puck.¹³¹ There have also been refinements in device settings; frequency and strength of stimulation and drug administration that can be specific to each patient.⁸⁵ Precision of stimulation has also increased, individuals are able to isolate single leads and independently change stimulation parameters to best suit their needs.⁸⁵ Devices equipped with accelerometers are also able to provide sleep and mobility data for research and custom stimulation specific to patient positioning.⁹¹ Many new devices are now magnetic resonance imaging (MRI) compatible which eliminates the concerns about future needs for patients to undergo MRI.⁸⁵ Charging abilities have also improved, shorter charging times, recharge from fully depleted battery, and better battery capacity fade have been developed.⁹¹ Proprietary combinations of device parameter waveforms have been created and are being developed as well (expert personal communication, June 27, 2018).

Beyond refinements in well-established neuromodulatory devices, newer types of less invasive stimulation are being explored. Transcutaneous and transcranial nerve stimulators offer less invasive, but also less targeted therapy.^{132,133} Peripheral nerve stimulation and peripheral nerve field stimulation continue to be researched and explored in clinical application. Experimental neuromodulatory interventions continue to be researched as well within animal models. Optical neuromodulation through optogenetics holds promise for even more targeted and specific interventions.¹³⁴

Changes in clinical practice are occurring in concert with the evolution of these technologies. As the understanding of medical conditions such as chronic pain, motor disorders, and psychological disorders increases, growing potential for neuromodulatory intervention is identified. Deep brain stimulation traditionally used in treatment of movement disorders is being investigated for use in treatment of psychological conditions such as treatment resistant depression, Tourette syndrome, and obsessive compulsive disorder (expert personal communication, June 21, 2018).

Combinations of neuromodulatory interventions are also being explored.⁸⁷

21 Implementation Analysis

Summary

- Four implementation options were developed based on the evidence
- These options include: discontinuing public funding for neuromodulation; maintaining the status quo; developing St. Paul's as the only center for neuromodulation; and developing a more coordinated approach to neuromodulation across the five regional health authorities

Based on the above evidence, policy and implementation options were developed for consideration. A list of possible options were presented to and discussed with a group of pain experts that included health professionals working in pain programs and organizations, and patients living with chronic pain in July 2018. The options were refined, based on this roundtable discussion, and are presented here along with general, implementation, and sustainability considerations in Table 26. Each of the four options is discussed in more depth below.

21.1 Discontinue public funding for new neuromodulation implants

The first option is to discontinue public funding for new neuromodulation implants. That is, those programs currently offering neuromodulation as an option to patients will no longer provide neuromodulation services. Although selecting this option would allow for healthcare resources to be reallocated, this would bring BC out of line with funding policies in other provinces and with guidelines and best practice recommendations for neuromodulation for pain, and standards of care in other jurisdictions. It also does not align with the evidence on clinical effectiveness for spinal cord stimulation and peripheral nerve stimulation for non-cancer pain and intrathecal pumps for cancer pain (see Table 10). Nor does it align with recommendations from most other HTA agencies, primarily for spinal cord stimulation (see Table 8).

Patients would not have access to this treatment option in BC through the publicly funded healthcare system. Those people with the resources to do so will have the option of accessing neuromodulation in other countries and potentially other provinces.

Table 26. Policy and Implementation Options

Policy and implementation Options	General Considerations	Implementation & Sustainability Considerations
<p>1. Discontinue public funding for new neuromodulation (NM) implants</p> <ul style="list-style-type: none"> - Those programs currently offering NM as an option to patients will no longer provide neuromodulation implants 	<ul style="list-style-type: none"> - Allows for healthcare resources to be reallocated - Does not align with: funding policies in most other provinces, guidelines & best practice recommendations, standards of care, recommendations from most other HTA agencies, & the research evidence on clinical effectiveness. - People living with severe chronic pain, for whom NM is an effective option, will not have access in BC. - People with resources will still have access to NM in other countries, and potentially other provinces, increasing inequity of access. - Patients will: increase use of pain medications, including opioids, and not have the opportunity to improve their quality of life - Some people may choose to end their lives, rather than live with severe pain 	<ul style="list-style-type: none"> - The 400+ people currently living in BC with NM to support their pain management will still need access to ongoing support, meaning that some BC chronic pain clinics will need to be able to provide this support - Patients having NM implants in other jurisdictions will continue to seek ongoing support in BC
<p>2. Maintain the status quo</p> <ul style="list-style-type: none"> - NM continues to be supported through some health authority budgets (Vancouver Coastal; Vancouver Island; and Northern Health) 	<ul style="list-style-type: none"> - No additional funding or other resources required to support NM - Local pain clinics that continue to provide NM as an option for their patients may be able to continue to do so into the near future - Partly aligns with: guidelines & best practice recommendations for neuromodulation for chronic pain, recommendations from most other HTA agencies, & the research evidence on the clinical effectiveness - Access to NM will continue to be challenging, and inequitable across the province - Some healthcare professionals currently doing implants, & supporting patients living with NM, may not be able to continue - Province-wide data collection will continue to be a challenge 	<ul style="list-style-type: none"> - Currently there are four BC hospital-affiliated pain programs providing some neuromodulation for pain - Increasingly, these programs offering some NM are struggling to maintain the status quo, so the sustainability of NM as a treatment option is at risk - It will be challenging to: take advantage of the improvements in technology & advancements in knowledge, to standardize practice across the province with respect to the kinds of NM offered, and patient selection processes used
<p>3. Develop St. Paul's as the only center for neuromodulation for pain in B.C.</p> <ul style="list-style-type: none"> - St. Paul's Complex Pain Program would be the quaternary site for BC NM; the only center that supports NM - Multi-disciplinary pain programs would be further developed in each of other four regional health authorities, with connections developed to St. Paul's to facilitate appropriate referrals 	<ul style="list-style-type: none"> - Additional funding would be required - Opportunity to better align with: guidelines & best practice recommendations, recommendations from most other HTA agencies, the research evidence on clinical effectiveness - NM as one treatment option for some people living with severe chronic pain will be more sustainable, and access will increase - Practice can be more easily standardized with respect to: the kinds of NM offered, and patient selection processes used, collection and analyze of data - Opportunity to: take advantage of the improvements in technology, and advancements in knowledge, and increase awareness of the indications and the benefits of neuromodulation - A greater % of people living with severe chronic pain would have less pain and live a fuller life 	<ul style="list-style-type: none"> - This model would be embedded in a BC Provincial Strategy for Chronic, Non-Cancer pain - More education would be needed, about the indications and the benefits of neuromodulation - Additional resources will be required to support the development of St. Paul's as the center of excellence for NM (e.g., increased OR time, increased clinic space, increased multi-disciplinary team support) - Some regional health authorities need to be willing to increase resources to support the development of multi-disciplinary team clinics - More neurosurgeons and pain physicians in NM will be required

<p>4. Develop a more coordinated approach to neuromodulation across the five regional health authorities</p> <ul style="list-style-type: none"> - A hub and spoke model would be developed with St. Paul's acting as the quaternary site and hub for neuromodulation - Multi-disciplinary pain programs would be further developed in each of other four regional health authorities, with connections developed with St. Paul's - At these spokes, less complex NM would be offered as an option, and some support provided for most patients with NM 	<ul style="list-style-type: none"> - Additional funding would be required - Opportunity to better align with: guidelines & best practice recommendations, recommendations from most other HTA agencies, the research evidence on clinical effectiveness - NM as one treatment option for some people living with severe chronic pain will be more sustainable, and access will increase - Patients with less complex needs will have the opportunity to get care closer to home (in comparison with options 1, 2 &3) - Practice can be more easily standardized with respect to: the kinds of NM offered, and patient selection processes used, collection and analyze of data - Opportunity to: take advantage of the improvements in technology, and advancements in knowledge, and increase awareness of the indications and the benefits of neuromodulation - A greater % of people living with severe chronic pain would have less pain and live a fuller life 	<ul style="list-style-type: none"> - This model would be embedded in a BC Provincial Strategy for Chronic, Non-Cancer pain - More education would be needed, about the indications and the benefits of neuromodulation as part of a pain management strategy for some people living with certain kinds of chronic pain, for both patients and healthcare professionals - Health Authorities would need to be willing to increase resources devoted to NM (e.g., space allocation, OR time, multi-disciplinary team support for patients) - To stimulate the development of NM capacity in all health authorities, training and mentoring will be required - Only those regional health authorities that have enough volume to maintain their implanting skills will do NM implants - More neurosurgeons and pain physicians in NM will be required: attracting and retaining these highly skilled physicians may be challenging, especially outside of major centers
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With respect to implementation and sustainability, the approximately 400 people living in BC with neuromodulation devices implanted in BC to support their pain management will still need access to ongoing support including neuromodulation revisions and replacements. It will be important that some BC pain clinics are still able to continue to provide this support to their patients. In the future, given that some people are likely to choose to go to other provinces or countries to get access to neuromodulation and/or those who have obtained implants in other provinces or countries will move to BC, there will be new patients living with neuromodulation devices that will expecting to get support in BC even though they had the devices implanted elsewhere.

21.2 Maintain the status quo

The second option is to maintain the status quo in BC. Currently there are four BC hospital-affiliated pain programs providing some neuromodulation for pain: one in the Vancouver Coastal health authority (St. Paul's), two on Vancouver Island (Royal Jubilee Hospital in Victoria & Nanaimo Regional Hospital), and one in the North (Prince George) with St. Paul's being the referral site for the most complex patients. Selecting this option would mean that no additional funding or other resources are required to support neuromodulation. Local pain clinics that provide neuromodulation as an option for their patients may be able to continue to do so into the near future. This option is more in alignment with guidelines & best practice recommendations for neuromodulation for chronic pain and standards of care in other jurisdictions and with the recommendations from most other HTAs. It also better aligns with the evidence on clinical effectiveness for both spinal cord stimulation and peripheral nerve stimulation for non-cancer pain and intrathecal pumps for cancer pain (see Table 10).

Those patients living with severe pain, where neuromodulation is an effective option, will continue to have limited access to neuromodulation; this means access to people living across BC will be inequitable. Currently, spinal cord stimulation devices can only be implanted and supported in the Vancouver Coastal and the Vancouver Island health authorities. Prince George currently only has funding to support the implantation of intrathecal pumps.

Some healthcare professionals currently doing implants, and supporting patients living with neuromodulation, may not be able to continue to do so. Increasingly, these programs offering

some neuromodulation as an option for select patients are struggling to maintain the status quo, so the sustainability of neuromodulation as a treatment option is at risk.

Finally, the development of better connections between the pain programs currently supporting neuromodulation in BC may continue to be a challenge. There is currently an interest in working together more collaboratively to standardize practice across the province with respect to the kinds of neuromodulation offered, and the patient selection processes used. There is also an interest in improving province-wide data collection on the numbers and types of patients undergoing different kinds of neuromodulation procedures, any complications, and results. Without more resources to actively support collaboration, it may be difficult to continue to build on this good work underway and to take advantage of the improvements in technology, and the increasingly sophisticated understanding of how neuromodulation for pain functions and for which types of pain it will be most effective.

21.3 Develop St. Paul's Complex Pain Program as the only center for neuromodulation for pain in BC

The third option is to develop St. Paul's Complex Pain Program as the quaternary site for neuromodulation; the only center that supports neuromodulation in BC. That is, St. Paul's would be the only center that does SCS and intrathecal pump implants and revisions and provides ongoing follow-up for all patients with spinal cord stimulators. Multi-disciplinary pain programs would also be further developed in each of other four regional health authorities, and connections developed with St. Paul's; intrathecal pump refills could be provided locally. This model would be embedded in a BC Provincial Strategy for Chronic Non-Cancer pain. Developing this center of excellence would provide an opportunity to better align with: guidelines and best practice recommendations, as well as standards of care, for neuromodulation for chronic pain; the recommendations from most other HTA agencies; and with the evidence on the clinical effectiveness for both spinal cord stimulation and peripheral nerve stimulation for non-cancer pain, and intrathecal pumps for cancer pain (see Table 10).

Additional funding would be required to support this option. For example, increased operating room time, increased clinic space, increased multi-disciplinary team support, including nursing staff, data collection support, and clinician education would all be needed. Some regional health authorities would need to be willing to increase resources to support the development of new multi-disciplinary team pain clinics, or increase the support for existing multi-disciplinary team

pain clinics. More neurosurgeons and pain physicians in neuromodulation, either anesthesiologists and/or physiatrists, will be required. Attracting and retaining these highly skilled physicians may be challenging, although perhaps mitigated in this option as the major technical expertise will be centralized in Vancouver.

Neuromodulation as one treatment option for some people living with severe chronic pain will be more sustainable, and access to neuromodulation will increase. Currently, St. Paul's sometimes struggles with accepting referrals from other health authorities for patients who may benefit from neuromodulation. This kind of centralization would provide opportunities:

- for practice to be more easily standardized with respect to the kinds of neuromodulation offered, and patient selection processes used;
- to improve awareness of the indications and the benefits of neuromodulation, by both healthcare providers and the public, which could increase which would improve timely access
- for easier collection and analysis of provincial data; and,
- to take advantage of improvements in technology, and the increasingly sophisticated understanding of how neuromodulation for pain functions and for which types of pain it is most effective.

21.4 Develop a coordinated approach to neuromodulation across the five regional health authorities

A fourth option for consideration is to develop a hub and spoke model for neuromodulation in BC, with St. Paul's acting as the hub. As in option number three, multi-disciplinary pain programs would be further developed in each of the other four regional health authorities, with connections developed with St. Paul's. At these spokes, neuromodulation for less complex patients would be available as an option and ongoing support provided for most patients living with neuromodulation devices, including both spinal cord stimulators and intrathecal pumps. In the near future, for example, any implants needing to be done by a neurosurgeon would be done at St. Paul's. As the provincial neuromodulation program matures, it might be possible to develop neurosurgical capacity in some of the other health authority programs. Again, this model would be embedded in a BC Provincial Strategy for Chronic Non-Cancer pain.

Additional funding would be required for both St. Paul's as the hub, and other health authority programs as the spokes for this collaborative delivery model. Specific resources required at St. Paul's would include more space and access to operating room time. Only those regional health authorities that have enough volume to maintain their implanting skills will do neuromodulation implants but ongoing support of these patients may still be able to be done locally with support from St Paul's. More neurosurgeons and pain physicians with neuromodulation capacity will be required; attracting and retaining these highly skilled physicians may be challenging, especially outside of major centers. As with option three, more clinician and patient education would be needed, about the indications and the benefits of neuromodulation as part of a pain management strategy for some people living with certain kinds of chronic pain. To stimulate the development of neuromodulation capacity in all health authorities, training and mentoring will be required.

This option would have similar impacts and opportunities to those outlined for option three; neuromodulation as one treatment option for some people living with severe chronic pain will be more sustainable; access to neuromodulation will increase and there will be more equitable access for patients across BC; and a greater percentage of people living with severe chronic pain would have less pain and have a better quality of life. The additional benefit of this option, over option number three, is that patients with less complex needs will have the opportunity to get neuromodulation implants and ongoing support closer to home.

Similar to the third option, this would improve alignment with: guidelines and best practice recommendations, standards of care in other jurisdictions, recommendations from other HTA agencies, and research on clinical effectiveness. It would also create opportunities related to standardization of practice, collection and analysis of data, improving awareness of the indications and the benefits of neuromodulation, and taking advantage of advances in technology and related knowledge.

22 Cost-Utility Analysis: Comparing Spinal Cord Stimulation to Conventional Medical Management

Summary:

- For rechargeable SCS devices with a **nine-year lifetime** used for pain management in patients with failed back surgery syndrome, SCS is associated with lower cost (\$119,342) than CMM (\$121,528), and greater QALYs (4.09 vs 2.65).
- For non-rechargeable SCS devices with a **four-year lifetime**, SCS is associated with greater cost (\$70,005) than CMM (\$56,726), and greater quality adjusted life years (1.56 vs 1.16). The cost per additional QALY gained through SCS in this scenario is \$33,198.
- Outcomes are sensitive to monthly costs associated with each management strategy, and the probability of reaching optimal health states with each strategy.

22.1 Purpose

To compare the cost-effectiveness of SCS to CMM from the perspective of the Canadian publicly funded healthcare system. To identify SCS clinical efficacy model inputs, a systematic review of randomized controlled trials was conducted. Of all populations that might benefit from SCS, failed back surgery patients were the only clinical subgroup of SCS patients with evidence reporting the outcomes required for the model. Therefore, only patients with failed back surgery syndrome were considered here. A time horizon of nine years was selected to match the device lifetime for rechargeable SCS devices.

22.2 Methods

22.2.1 Model Overview

This model utilizes a randomized controlled trial published by Kumar et al.¹³⁵ for transition probabilities. Eligibility criteria for the trial and this model are: patients must suffer neuropathic pain of radicular origin (radiating in dermatomal segments L4 and/or L5 and/or S1) predominantly in the legs of at least 5/10 on a visual analogue scale for at least six months after a minimum of one anatomically successful surgery for a herniated disc.¹³⁵ Participants randomized to SCS undergo a trial of the technology, and if successful went on to receive an implantable Synergy™ neurostimulator (Medtronic, Inc., Minneapolis, MN, as cited in).¹³⁵ SCS trial success was defined as overlap of at least 80% of their pain with stimulation-induced paresthesia and at least 50% leg pain relief.¹³⁵ The CMM strategy included oral medications (e.g.: opioids, non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsant or antiepileptic agents, etc.),

nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care.¹³⁵

A decision tree was developed for the first six months of follow-up, and a Markov process simulated the remainder of the device lifetime (Figure 19). Two main outcomes were included: optimal health and suboptimal health. Optimal health states were defined as a 50% or greater reduction in baseline pain measured with a visual analogue scale. Suboptimal health states were defined as any reduction in baseline pain of less than 50%. In the SCS strategy, patients first receive a trial implant. For the patients that have a successful trial of SCS, or a pain reduction of 50% or greater compared to baseline pain measured with a visual analogue scale, a device is implanted and patients move directly to an optimal health state. Patients that had an unsuccessful trial of SCS received CMM and the same transition probabilities as patients in the CMM strategy were applied. Based on expert opinion, it was assumed that patients achieved stability of outcomes from the beginning of the second year onward and transitions were limited to remaining in the same health state or transitioning to death. Thus, patients in both arms then continue over the lifetime of the device with patients exposed to an ongoing risk of death. Markov model cycle length was six months.

22.2.2 Model Inputs

Sources for transition probabilities were identified through the previously described systematic review of clinical effectiveness of SCS in non-cancer patients (section 11). Transition probabilities for the decision tree and first cycle of the Markov process are presented in Table 27. Many transition probabilities rely on a multinational randomized controlled trial that included participants in Canada, Europe, Australia and Israel.¹³⁵ Costs and utility values for model health states rely upon observational data collected in Saskatchewan.¹³⁶ The probability of death from any health state was derived from the overall mortality rate in Canada in 2016.¹³⁷ Model inputs were selected to align with the perspective of a Canadian publicly funded healthcare system.

Figure 19. Model Diagram SCS and CMM

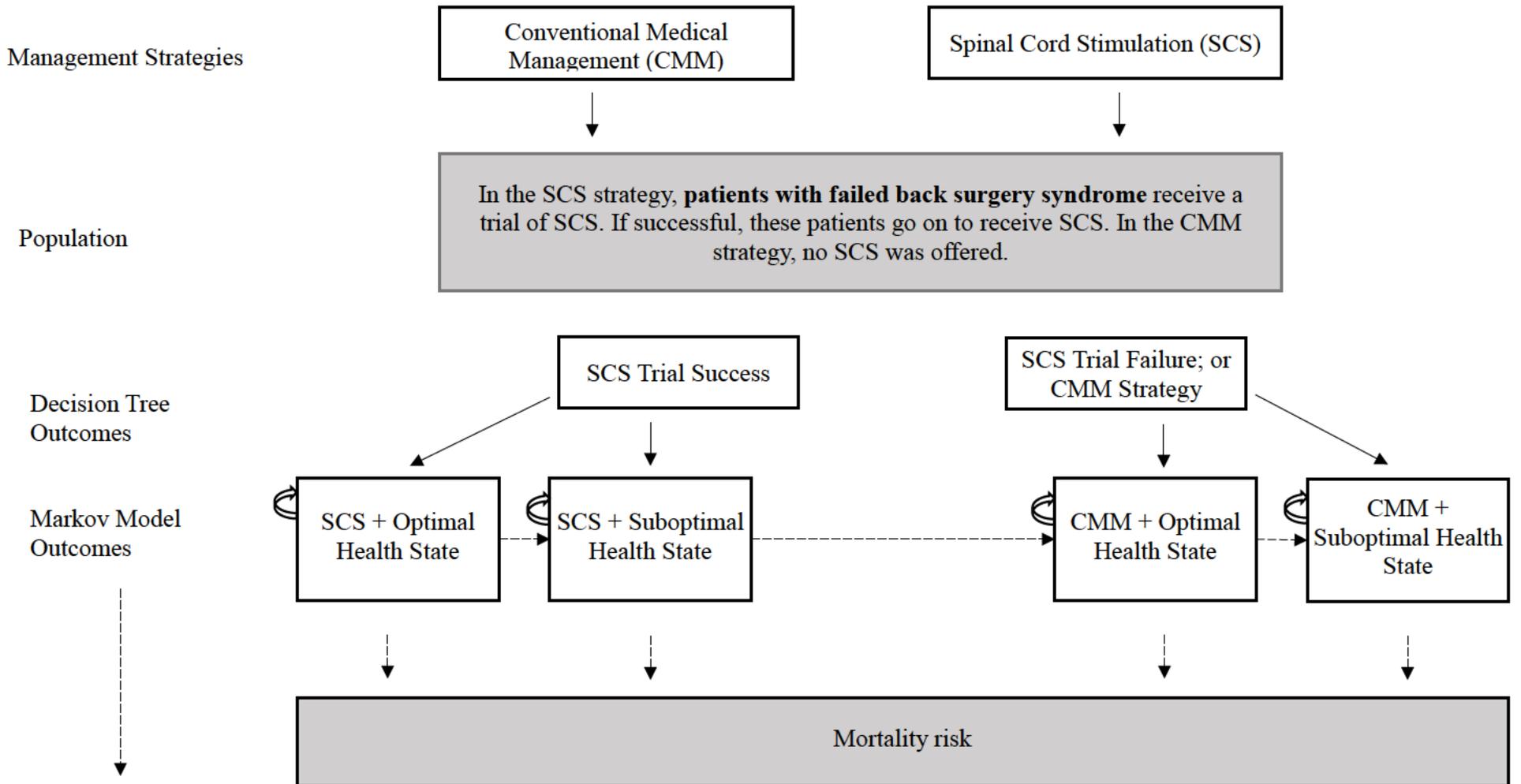


Table 27. Model Parameters

Model Inputs	Mean	Standard Deviation	Sources
Months 0-6 Transition Probabilities: SCS trial success CMM optimal health CMM Sup-optimal health	0.79 0.1 0.9	0.04 0.04 0.04	Kumar et al. 2007; ¹³⁵ North et al., 2005 ¹⁴²
Months 6-12 Transition Probabilities: SCS optimal health SCS optimal health to SCS sub-optimal health CMM optimal health CMM optimal health to CMM sub-optimal health Death	0.6 0.40 0.27 0.72 0.00369	0.08 0.04 0.07 0.07 0.0000102	Kumar & Rizvi, 2013; ¹³⁶ Kumar et al., 2007; ¹³⁵ Statistics Canada ¹³⁷
Months 12- End Transition Probability: Death	0.00369	0.0000102	Statistics Canada ¹³⁷
Costs: SCS trial SCS device and implant procedure SCS complications SCS maintenance SCS adjunctive therapy SCS pharmacotherapy CMM evaluations CMM imaging CMM pharmacotherapy CMM alternative therapy CMM intermittent hospitalization	\$4,415 \$24,376 \$500 \$3,397 \$1,211 \$286 \$841 \$1,554 \$857 \$2,523 \$1,607	\$552 \$3,047 \$62 \$424 \$151 \$35 \$105 \$194 \$107 \$315 \$201	Kumar & Rizvi, 2013 ¹³⁶
Utility of health states: SCS optimal health SCS sub-optimal health CMM optimal health CMM sub-optimal health	0.62 0.41 0.54 0.32	0.08 0.05 0.07 0.04	Kumar & Rizvi, 2013 ¹³⁶

22.2.3 Cost Inputs

All costs associated with health states are from a study by Kumar and Rizvi, 2013.¹³⁶ This study was conducted in Regina, Saskatchewan, and included data from 184 patients with FBSS.¹³⁶ All costs collected in this study reflected the costs to the publicly funded healthcare system in Saskatchewan.¹³⁶ Costs were inflated to 2017 Canadian dollars using the consumer price index.¹³⁸ Costs of SCS trial included consultations by family physicians, orthopedic surgeons, psychiatrists, social workers, neurologists, and neurosurgeons, as well as diagnostic workup.¹³⁶ Costs of SCS implantation include surgeon and anesthesia fees, operating room fees, hospital admission, and equipment.¹³⁶ Device costs are based on implantation of 2 x 8 octad percutaneous

leads with a RestoreAdvanced™ rechargeable pulse generator (Medtronic of Canada, Ltd).¹³⁶ Costs of SCS complications, SCS maintenance, SCS adjunctive therapy, and SCS pharmacotherapy occur in each six-month model cycle. SCS maintenance costs include nursing care, physician care, and some medication.¹³⁶ SCS adjunctive therapy costs include acupuncture, physiotherapy, massage, and chiropractic services.¹³⁶ SCS pharmacotherapy costs include prescription medications and dispensing costs.¹³⁶ Costs are aggregated in the study by Kumar and Rizvi,¹³⁶ and it was not possible to unbundle the costs within any of these categories.

Costs for CMM evaluations, CMM imaging, CMM pharmacotherapy, CMM alternative therapy, and CMM intermittent hospitalization were applied during each model cycle to all CMM health states. Costs of CMM evaluations included assessment by health care professionals such as family physicians, orthopedic surgeons, psychiatrists, social workers, neurologists, and neurosurgeons.¹³⁶ CMM imaging costs include computed tomography, magnetic resonance imaging, and ultrasound studies.¹³⁶ Alternative therapy costs for CMM include epidural steroid blocks, trigger point injections, nerve blocks, physiotherapy, chiropractic treatments, massage therapy, and acupuncture.¹³⁶ CMM pharmacotherapy costs include prescription medications and dispensing costs.¹³⁶ And CMM intermittent hospitalization treatment costs are for the treatment of acute breakthrough pain.¹³⁶

22.2.4 Utility Inputs

Utility values for health states were collected at six months of follow-up in the study by Kumar and Rizvi.¹³⁶ Utility was measured with the EuroQol (EQ-5D) questionnaire.¹³⁶ The utility value associated with the SCS optimal health state was 0.62, and the utility value for CMM optimal health was 0.54.¹³⁶ Utility values associated with suboptimal health states were 0.41 and 0.32 in the SCS and CMM strategy, respectively.¹³⁶

22.2.5 Model Validity

Face validity of this model relies on the published model by Kumar and Rizvi.¹³⁶ To establish internal validity, calculations were hand-checked. Inputs were also adjusted to ensure that the outputs changed in the expected direction. Similar to Kumar and Rizvi,¹³⁶ it was conservatively assumed that suboptimal pain outcomes did not change cost or QALY outcomes associated with health states.

22.2.6 Uncertainty Analyses

In one-way sensitivity analysis, all variables were independently increased and decreased by one standard deviation. In the base-case analysis, a nine-year time horizon was selected to match the expected device lifetime for a rechargeable SCS device (¹³⁹ as cited in ¹³⁶). In scenario analysis, a shorter time horizon of four years is explored to match the lifespan of non-rechargeable SCS devices (¹⁴⁰ as cited in ¹³⁶). Parameter uncertainty was explored through 1,000 iterations of probabilistic sensitivity analysis. In probabilistic sensitivity analysis beta-binomial distributions were assigned to transition probabilities with two possible outcomes, and Dirichlet distributions were assigned to transition probabilities with three or more possible outcomes. Gamma distributions were assigned to cost parameters, and normal distributions were assigned to utility values. All costs and QALY outcomes were discounted at 1.5% per year, as recommended by the Canadian Agency for Drugs and Technology in Health.¹⁴¹

22.3 Results

22.3.1 Validity

This work uses the model structure previously published by Kumar and Rizvi¹³⁶ and relies on this publication for face validity. Assumptions around transition probabilities after the first year were validated with expert opinion. Internal validity of the model was established through hand-checking of calculations, and agreement between adjustment of inputs and expected direction of change of outputs. Agreement in output changes between expectations and observed values in one-way sensitivity analysis also supported internal validity of the model.

22.3.2 Base Case Incremental Cost-utility Ratios

Over a nine-year time horizon, the expected cost of SCS and CMM are \$119,342 and \$121,528 respectively. QALYs associated with SCS are 4.09 and with CMM are 2.65. As the costs of CMM are higher than those of SCS and CMM is less effective than SCS (fewer QALYs), CMM is dominated (Table 28).

Table 28. Deterministic model results with nine-year device lifetime

Strategy	Cost (\$)	Incremental Cost (\$)	QALYs	Incremental QALYs	Incremental Cost Effectiveness Ratio (\$/QALY)
SCS	\$119,342	-	4.09	-	-
CMM	\$121,528	\$2,186	2.65	-1.44	Dominated

22.3.3 *Uncertainty Analysis*

In one-way sensitivity analysis, all variables were independently increased and decreased by one standard deviation to explore model sensitivity to inputs (Figure 20). The model was most sensitive to the probability of reaching an optimal health state with SCS. In the base case, the incremental cost-effectiveness ratio (ICER) was -\$1,518 per additional QALY; where the negative ICER reflects the negative incremental QALYs. When the probability of reaching an optimal health state with SCS is increased and decreased by one standard deviation, the incremental cost effectiveness ratio ranged from \$1,782 (here SCS is more expensive and more effective than CMM) to -\$6,597 (due to negative incremental QALYs).

The model was also sensitive to costs associated with SCS maintenance and CMM alternative therapy, which were the highest costs incurred in each model cycle for each strategy. In the base case, costs of SCS maintenance incurred every six months for patients that had SCS devices were \$3,397. When increased by one standard deviation, to \$3,821, the cost of the SCS strategy increased to \$124,856; and when decreased by one standard deviation, to \$2,972, the cost of the SCS strategy decreased to \$113,828. The baseline value of CMM alternative therapy was \$2,523, and this cost was incurred every six months. When the cost of CMM alternative therapy was increased by one standard deviation to \$2,838, the incremental cost of CMM compared to SCS increased from \$2,186 to \$6,280. When the cost of CMM alternative therapy was decreased by one standard deviation to \$2,208, the CMM strategy cost \$1,908 less than SCS.

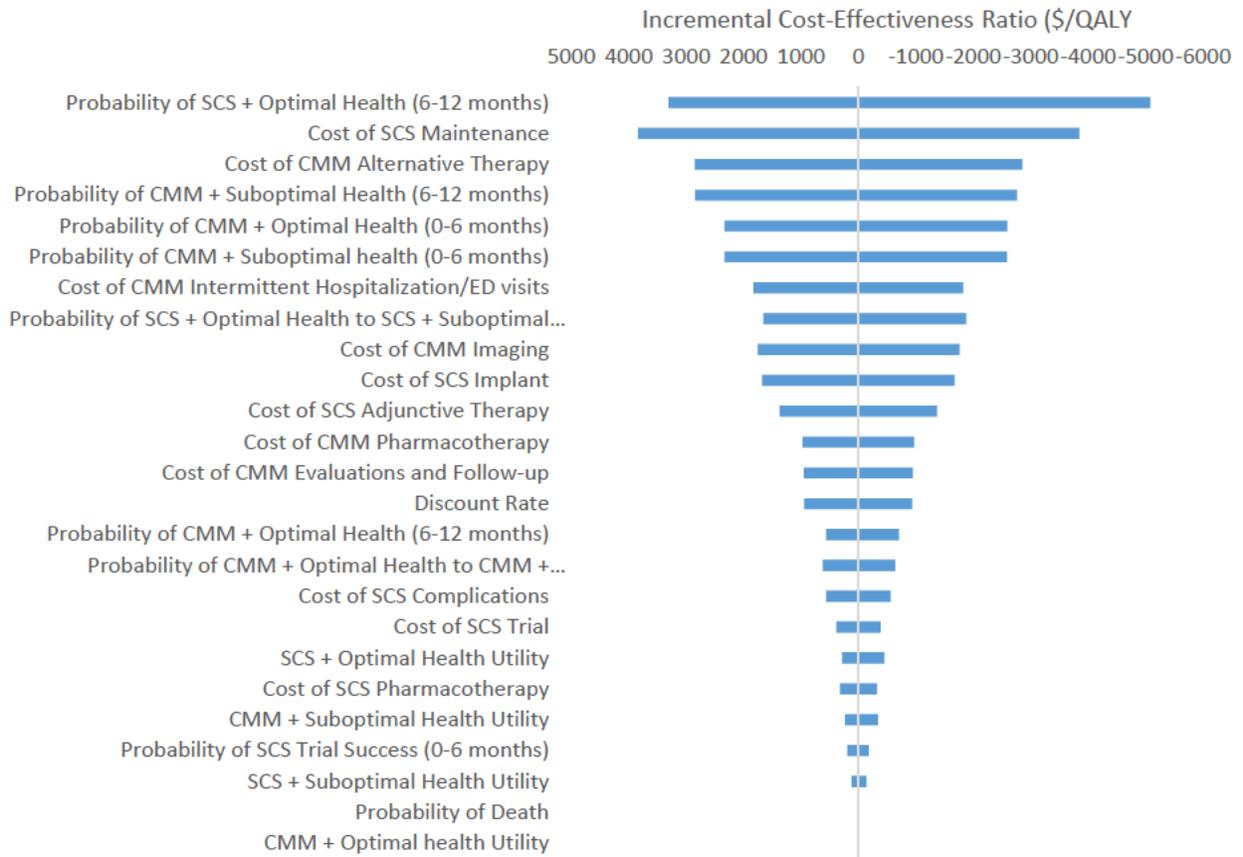
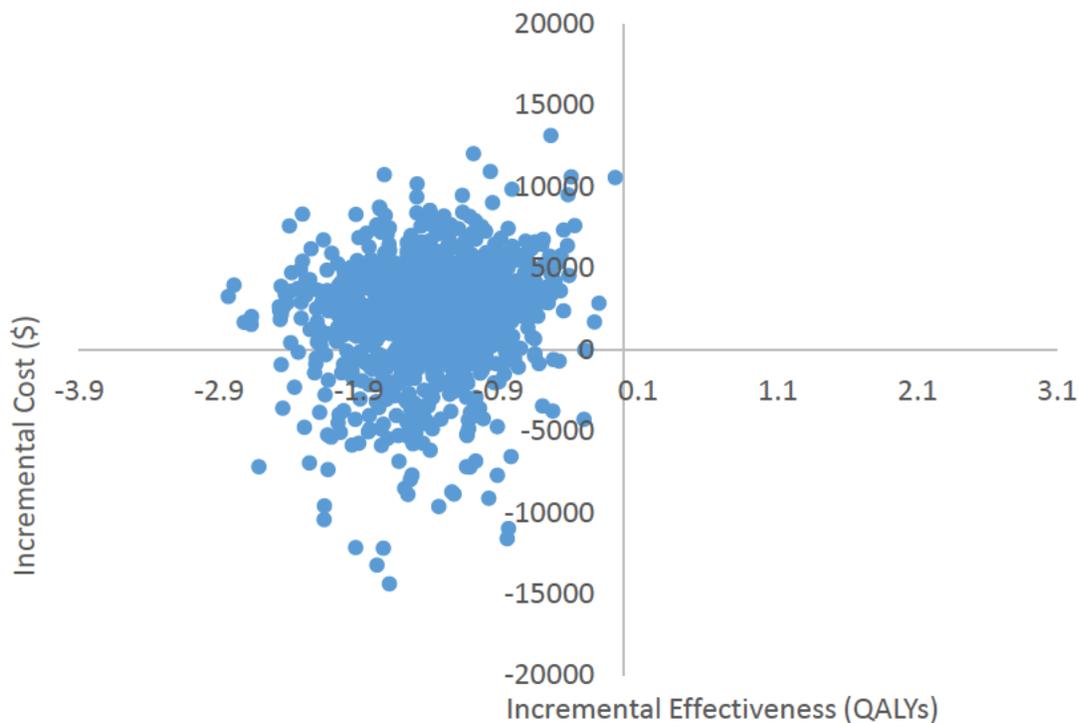


Figure 20. One-way sensitivity analysis. Extreme values tested were the mean plus/minus one standard deviation

The effect of using non-rechargeable SCS devices with a lifespan of four years was tested in scenario analysis. In this scenario, the expected cost of CMM was \$56,726 compared to \$70,005 with SCS. CMM resulted in 1.16 QALYs and SCS resulted in 1.56 QALYs. The cost per QALY gained with SCS compared to CMM over four years, was \$33,198. After the costs of SCS trial and implant are incurred initially, costs of SCS every six months are lower than the cost of CMM. Costs between the two strategies are approximately equivalent when the device lifetime is eight years. When the SCS device lifetime is longer than eight years, the SCS strategy is less costly than the CMM strategy.

After 1,000 iterations of probabilistic sensitivity analysis, greater than 99% convergence was achieved. In all iterations of probabilistic sensitivity analysis SCS resulted in greater QALYs than CMM. In 78.1% of iterations SCS was less expensive than CMM and in 21.9% of iterations SCS was more expensive than CMM (Figure 21).

Figure 21. One thousand iterations of probabilistic sensitivity analysis



22.4 Conclusions

In the base case analysis, SCS results in reduced cost and greater QALYs than CMM. One-way sensitivity analysis shows that the model is sensitive to the costs associated with each health state. Probabilistic sensitivity analysis also suggests that SCS is more effective than CMM; however, much uncertainty remains in the incremental cost of SCS compared CMM.

One major source of uncertainty in this model was the source used for costs associated with health states. All costs for health states were from a 2013 study by Kumar and Rizvi.¹³⁶ The study by Kumar and Rizvi¹³⁶ takes the perspective of a publicly funded healthcare system for costs, which is congruent with the perspective taken in this analysis. It is also known that the field of neuromodulation is rapidly evolving, and this cost data is likely outdated. Furthermore, it was assumed that suboptimal health states with pain reductions of less than 50% had the same costs as optimal health states in which pain was reduced by at least 50%. This assumption may or may not be realistic.

This model also relies upon the model structure described by Kumar and Rizvi,¹³⁶ however insufficient data was provided to entirely recreate their model. This model improves upon the model described by Kumar and Rizvi¹³⁶ through the use of transition probabilities from a randomized controlled trial; but data for costs, utility, and transition probabilities no longer come from the same study sample. Transition probabilities are heavily reliant upon a randomized controlled trial by Kumar et al.¹³⁵ which included 100 patients. Confidence in estimates used for transition probabilities would be increased with additional evidence to incorporate into analysis.

After high initial costs associated with device implantation, costs for maintenance with SCS are lower than with CMM. At every time point, patients in the SCS strategy were expected to experience greater QALYs than those in the CMM strategy. In order for the two strategies to be cost-neutral, the device lifetime needs to be at least eight years. Beyond this point, SCS is both less costly and results in greater QALYs than CMM. However, much uncertainty remains in cost outcomes for these patients, which are only representative for patients with FBSS. It is known that SCS is used for other indications in BC, including but not limited to CRPS and angina. Future data collection of costs associated with health states in BC would improve the ability to make evidence-based resource allocation decisions in this context.

In the event that costs associated with health states are deemed unreasonable, an excel file is included in Appendix P with the title “Neuromodulation and FBSS.xlsm.” This copy of the model allows the user to input their own costs associated with health states, and will return immediate results. If the standard error is also known, the user is invited to enter both the mean and standard error, and the probabilistic sensitivity analysis can also be easily recreated.

23 Cost-Effectiveness Analysis: Comparing Intrathecal Pumps to Comprehensive Medical Management

Summary:

- Over a four year time horizon in patients with refractory cancer pain, intrathecal pumps are associated with greater cost (\$65,408) than CMM (\$28,145), and greater life years (0.76 vs 0.47).
- Outcomes are sensitive to monthly costs associated with each management strategy, and differing probabilities of death associated with each strategy in the base case analysis. If mortality risk associated with CMM is the same as that of intrathecal pumps the cost of the CMM strategy increases to \$45,795 and the cost of the intrathecal pump strategy is unchanged, with 0.76 life years expected for each strategy.
- In 94.8% of iterations of probabilistic sensitivity analysis intrathecal pump resulted in greater life years and cost than CMM.
- Poor reporting of trial outcomes underlying transition probabilities and limited cost data for this patient population inhibit confidence in model findings. Future data collection that includes clinical endpoints, utility, and cost data with the goal of informing economic evaluation could strengthen evidence-based resource allocation decisions in this context.

23.1 Purpose

To compare the cost-effectiveness of intrathecal pumps to CMM in patients with refractory cancer pain, from the perspective of a Canadian publicly funded healthcare system.

Methods

23.1.1 Model Overview

To inform model development, systematic reviews of clinical effectiveness of intrathecal pumps in cancer and non-cancer populations were conducted (section 14). All included studies in non-cancer populations compared therapeutic agents to placebo delivered through an intrathecal pump; and were not appropriate for incorporation into a model comparing intrathecal pumps to CMM for the management of pain.

This model simulates the patient population reported with a randomized controlled trial.¹⁴³ Eligible patients were those with documented cancer, visual analogue scale pain scores consistently $\geq 5/10$ despite pain management by their oncologist, on at least 200mg of oral morphine or the equivalent, and with an expected lifespan of at least 3 months.¹⁴³ The two pain management strategies compared in this trial were CMM and intrathecal pump. In the CMM, strategy, pain was managed according to guidelines described in “Clinical Practice Guideline Number 9: Management of Cancer Pain” (¹⁴⁴ as cited in ¹⁴⁵). This strategy included all pain

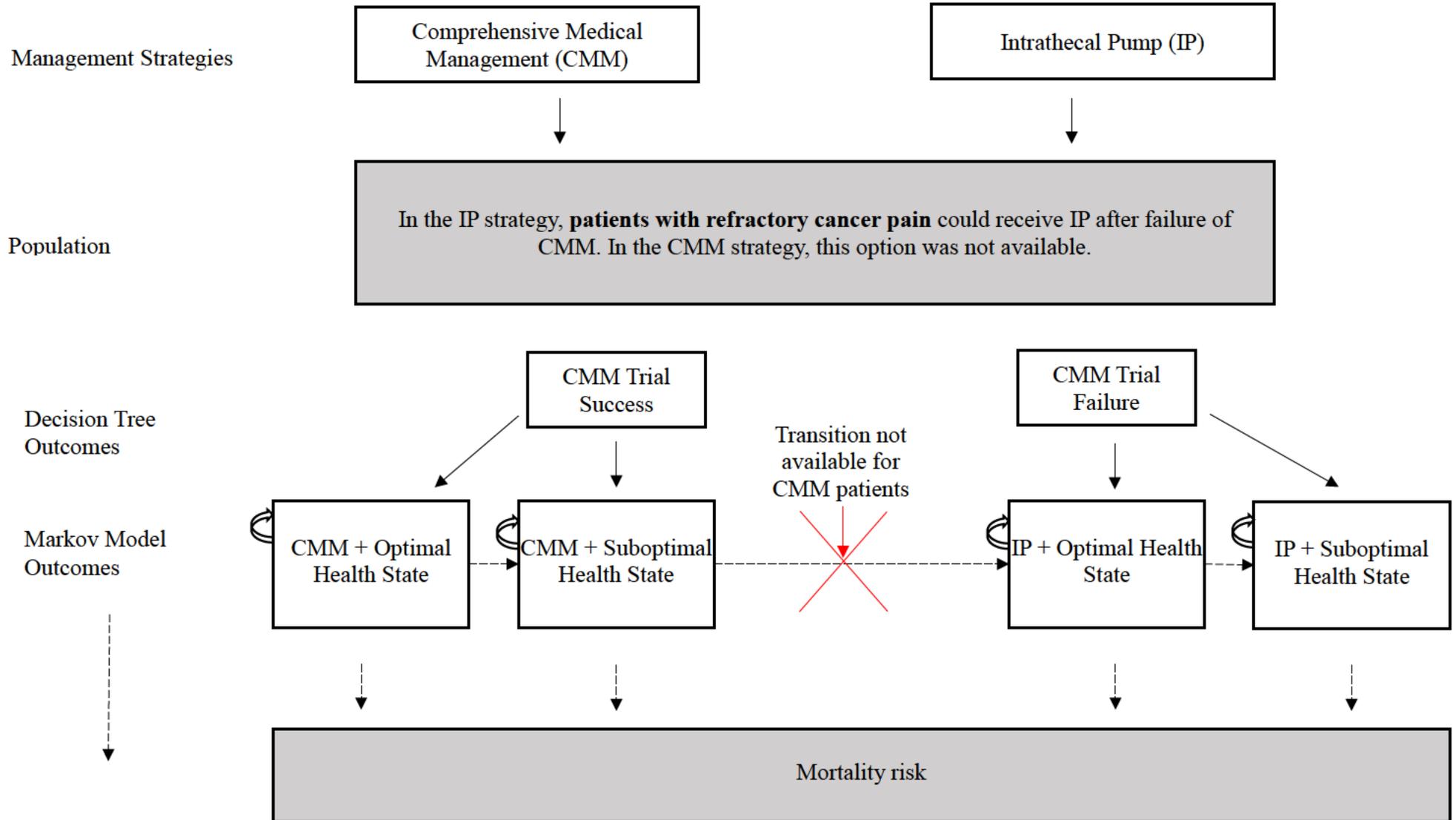
therapies except spinally administered drugs, cordotomy, or other neurosurgical interventions.¹⁴⁵ In the intrathecal pump strategy, the patients that did not achieve sufficient pain relief with CMM had the option to also receive an intrathecal pump.¹⁴⁵ Those who received the intrathecal pump started with morphine, but could receive other analgesics if morphine was ineffective.¹⁴⁵

A decision tree was used to represent the first four weeks of follow-up, and a Markov process was used to represent the remainder of the time horizon (Figure 22). In the intrathecal pump strategy, patients first undergo a trial of CMM. For the patients that have a successful trial of CMM, or a pain reduction of 20% or greater compared to baseline pain measured with a visual analogue scale, they would move directly to an optimal health state while receiving CMM. Optimal health states were defined as a 20% or greater reduction in baseline pain measured with a visual analogue scale. Patients that had an unsuccessful trial of CMM received an intrathecal pump. For patients in the intrathecal pump strategy, there were five possible health states: CMM and optimal health, CMM and suboptimal health, intrathecal pump and optimal health, intrathecal pump and suboptimal health, or death. Suboptimal health states were defined as any reduction in baseline pain of less than 20%. A time horizon of four years was selected. At this time point, greater than 99% of the model cohort has died.

23.1.2 Model Inputs

All transition probabilities are from a RCT comparing intrathecal pumps to CMM in patients with refractory cancer pain.¹⁴³ This source was identified through the previously described systematic review of clinical effectiveness of intrathecal pumps in patients with cancer (section 14). The probability of death from each health state was derived from the same RCT and differed by management strategy.¹⁴⁵ To match trial reporting of pain outcomes, Markov model cycle length was four weeks. Transition probabilities for the decision tree are included in Table 29. Transition probabilities for each strategy are included in Table 30. After the decision tree

Figure 22. Model Diagram Intrathecal Pump and CMM



representing the first four weeks, it was assumed that transition probabilities between health states were consistent over time.

Table 29. Transition probabilities for weeks 0-4

Decision Tree Probabilities (weeks 0-4)	Mean	Standard Deviation	Source
CMM trial success	0.30	0.054	Smith et al., 2002; ¹⁴⁵
CMM Death	0.14	0.035	
Intrathecal Pump Optimal Health	0.80	0.006	Smith et al., 2005 ¹⁴³
Intrathecal Pump Suboptimal Health	0.10	0.006	
Intrathecal Pump Death	0.09	0.029	

Table 30. Transition probabilities for weeks 4-196

Markov Model Transition Probabilities (weeks 4-196)	Mean	Standard Deviation	Source
Intrathecal Pumps:			
Remain in CMM Optimal Health	0.650	0.005	Smith et al., 2005 ¹⁴³
Transition from CMM Optimal Health to CMM Suboptimal Health	0.260	0.005	
Remain in CMM Suboptimal Health	0.864	0.003	
Transition from CMM Suboptimal Health to Intrathecal Pump Optimal Health	0.041	0.002	
Transition from CMM Suboptimal Health to Intrathecal Pump Suboptimal Health	0.005	0.001	
Remain in Intrathecal Pump Optimal Health	0.805	0.008	
Transition from Intrathecal Pump Optimal Health to Suboptimal Health	0.105	0.006	
Remain in Intrathecal Pump Suboptimal Health	0.910	0.006	
Death	0.090	0.03	
Comprehensive Medical Management:			
Remain in CMM Optimal Health	0.614	0.005	Smith et al., 2005 ¹⁴³
Transition from CMM Optimal Health to CMM Suboptimal Health	0.245	0.005	
Remain in CMM Suboptimal Health	0.859	0.004	
Death	0.141	0.03	

23.1.3 Cost Inputs

All costs associated with health states are from a study by Brogan et al.¹⁴⁶ In the study by Brogan et al.,¹⁴⁶ cost data was collected before and after intrathecal pump implantation in a cohort of 36 participants. Pre-implantation costs were assumed to reflect CMM strategy costs, and post-

implantation costs were assumed to reflect intrathecal pump strategy costs. The cost of intrathecal pump implantation from Brogan et al.¹⁴⁶ reflects the Medicare allowable rate for Salt Lake City, Utah in the United States in 2011. This cost and all others were converted to 2017 Canadian dollars using purchasing power parity and the consumer price index for all goods.^{138,147} Mean and standard deviation costs per day were multiplied by 28 to give expected values over each 28-day model cycle (Table 31).

Table 31. Model Costs

Description	Mean	Standard Deviation
Intrathecal Pump Implant	\$47,469.10	NA
Intrathecal Medications and Refills (incurred during each cycle)	\$1,336.72	\$2,048.20
Additional Medications for Intrathecal Pump Strategy (incurred during each cycle)	\$218.96	\$1,177.40
Intrathecal Pump Maintenance (incurred during each cycle)	\$1,264.48	\$2,050.44
CMM Medication Costs (incurred during each cycle)	\$4,624.48	\$9,214.8

23.1.4 Effectiveness Inputs

Utility associated with health states for patients with refractory cancer managed with intrathecal pump and CMM was not available. Therefore, no quality weight was applied to survival. The measure of effectiveness used in this analysis is life years, and reflects only the length of life.

23.1.5 Model Validity

Interviews with clinicians suggested that intrathecal pump was considered only when a patient had exhausted every other possible option, which underlies the model structure. To establish internal validity, calculations were hand-checked. Inputs were also adjusted to ensure that the outputs changed in the expected direction. It was conservatively assumed that suboptimal pain outcomes did not change costs associated with health states.

23.1.6 Uncertainty

In one-way sensitivity analysis, all variables except for implantation of intrathecal pump were independently increased and decreased by one standard deviation. In this analysis, cost of intrathecal pump implantation was \$47,469.10¹⁴⁶. Because no measures of variation for this cost were available, intrathecal pump implantation was treated as a fixed cost. In one-way sensitivity

analysis, this cost was increased and decreased by 25%. When reduction of deterministic model parameters by one standard deviation resulted in a value of less than zero, zero was used instead.

In scenario analysis, the effect of having the same risk of mortality with both strategies was explored. Here, the risk of mortality with the CMM strategy was assumed to be equivalent to the risk of mortality in the intrathecal pump strategy.

Parameter uncertainty was explored through 1,000 iterations of probabilistic sensitivity analysis. In probabilistic sensitivity analysis beta-binomial distributions were assigned to transition probabilities with two possible outcomes, and Dirichlet multinomial distributions were assigned to transition probabilities with three or more possible outcomes. Gamma distributions were assigned to cost parameters. All costs and life year outcomes were discounted at 1.5% per year, as recommended by the Canadian Agency for Drugs and Technology in Health.

23.2 Results

23.2.1 Validation

The structure of this model relies on information gathered during clinician interviews, which suggested that intrathecal pump is not considered unless a patient with refractory cancer pain has exhausted all medical management options. Internal validity of the model was established through hand-checking of calculations, and agreement between adjustment of inputs and expected direction of change of outputs. Agreement in output changes between expectations and observed values in one-way sensitivity analysis also supported internal validity of the model.

23.2.2 Base Case Incremental Cost-utility Ratio

Over a four year time horizon, the expected cost of intrathecal pump and CMM are \$65,408 and \$28,145 respectively. Life years associated with intrathecal pump are 0.76 and with CMM are 0.47. The ICER, interpreted as the additional cost per year of life gained, is \$126,925 (Table 32).

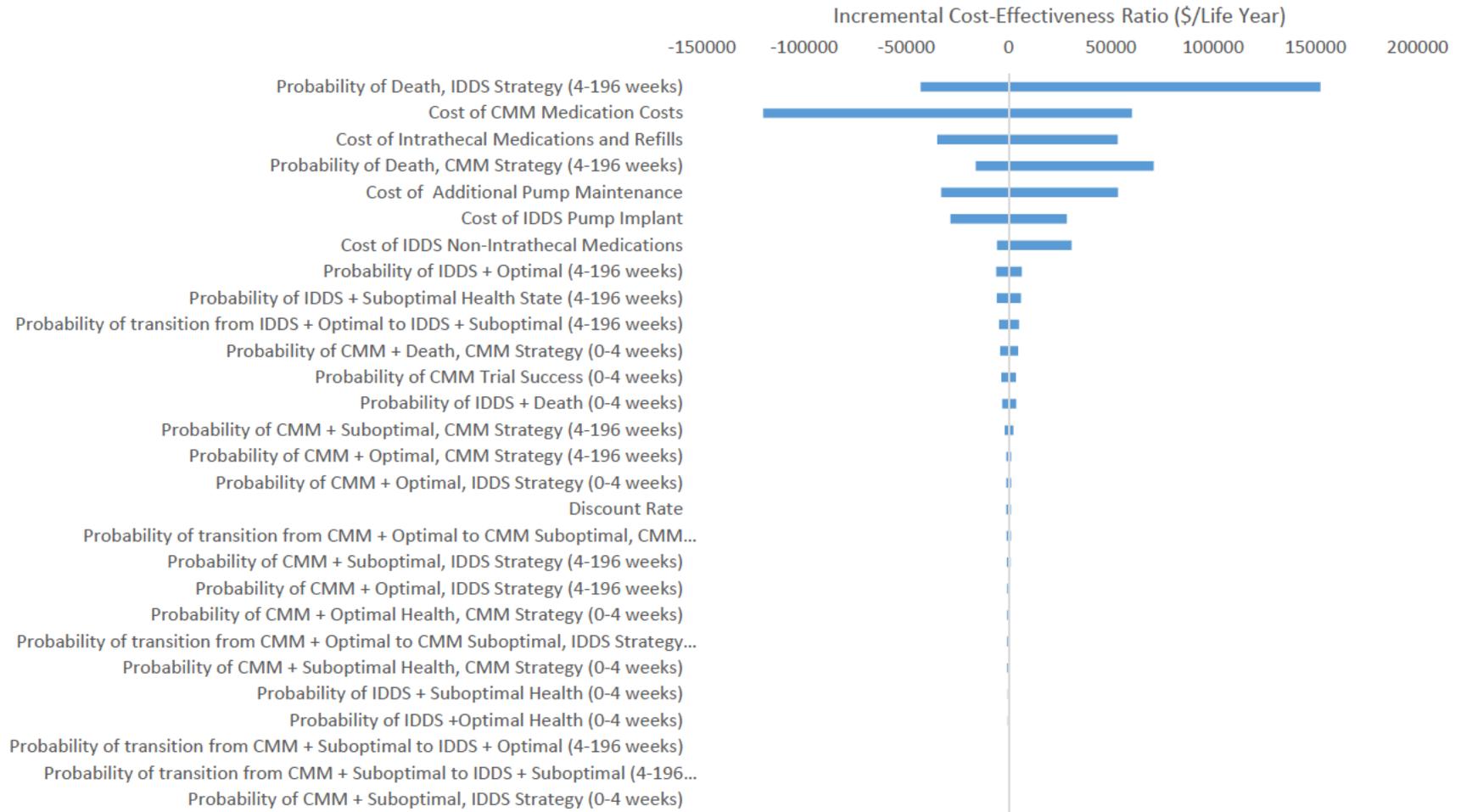
Table 32. Deterministic model results

Strategy	Cost (\$)	Incremental Cost (\$)	Life Years	Incremental Life Years	Incremental Cost Effectiveness Ratio (\$ per additional life year)
CMM	\$28,145	-	0.47	-	-
Intrathecal Pump	\$65,408	\$37,263	0.76	0.29	\$126,925

In one-way sensitivity analysis, all variables were independently increased and decreased by one standard deviation to explore model sensitivity to inputs (). The model was most sensitive to the probability of death with the intrathecal pump strategy. In the base case, the ICER was \$126,925 per additional life year. When the probability of death with an intrathecal pump was increased and decreased by one standard deviation, the ICER ranged from \$279,294 to \$83,938 per additional life year.

The model was also highly sensitive to costs associated with CMM medications and intrathecal pump medications and refills, which were the highest costs incurred in each model cycle for each strategy. In the base case, costs of medications in the CMM strategy incurred every four weeks were \$4,624. When increased by one standard deviation, to \$13,839, the cost of the CMM strategy increased to \$84,227; and when decreased by one standard deviation, to \$0, the cost of the CMM strategy decreased to \$0. The baseline value for the cost of intrathecal pump medications and refills was \$1,337, and was incurred every four weeks. When the cost of intrathecal pump medications and refills was increased by one standard deviation to \$3,385, the cost of the intrathecal pump strategy increased from \$65,408 to \$81,051. When the cost of intrathecal pump medications and refills was decreased by one standard deviation to \$0, the intrathecal pump strategy cost \$55,198.

Figure 23. One-way sensitivity analysis. Extreme values tested were the mean plus/minus one standard deviation.



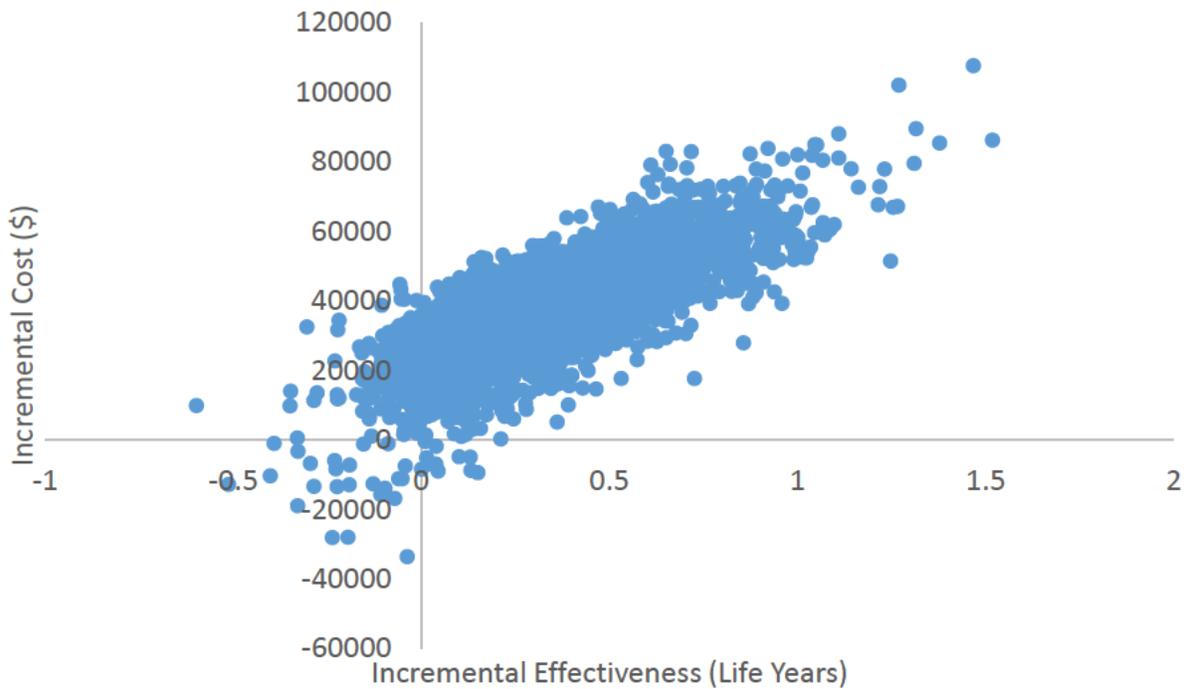
When the risk of mortality with the CMM strategy was set to the same value as the intrathecal pump strategy, the difference in life years becomes zero; both strategies result in 0.76 life years. The cost of the CMM strategy increases to \$45,795 and the cost of the intrathecal pump strategy is unchanged (Table 33). In this scenario, the proportion of patients in optimal health states in the intrathecal pump strategy is greater than the proportion of patients in optimal health states in the CMM strategy in all model cycles.

Table 33. Scenario analysis results

Strategy	Cost (\$)	Incremental Cost (\$)	Life Years	Incremental Life Years	Incremental Cost Effectiveness Ratio (\$ per additional life year)
CMM	\$45,795	-	0.76	-	-
Intrathecal Pump	\$65,408	\$19,613	0.76	0	NA

After 4,000 iterations of probabilistic sensitivity analysis, greater than 99% convergence was achieved. In 94.8% of 4,000 iterations of probabilistic sensitivity analysis intrathecal pump resulted in greater cost and greater life years than CMM. In 4.3% of iterations intrathecal pump resulted in greater cost and fewer life years than CMM. In 0.6% of iterations, intrathecal pump resulted in reduced cost and fewer life years than CMM, and in 0.3% of iterations intrathecal pump resulted in reduced cost and greater life years than CMM (Figure 24).

Figure 24. Four thousand iterations of probabilistic sensitivity analysis. Incremental outcomes calculated as intrathecal pump minus CMM



23.3 Conclusions

Compared to CMM, use of an intrathecal pump resulted in greater life years at a greater cost for patients with refractory cancer pain. One-way sensitivity analysis suggests that model outcomes are sensitive to the costs associated with health states, and the probability of death associated with each strategy. The model was heavily based on a trial described by Smith et al.¹⁴⁵ Results of this trial suggest that the improved survival for participants randomized to intrathecal pump is connected to reductions in drug toxicity also observed with intrathecal pump.¹⁴⁵

However, the connection between interventions and survival is not clear. Although participants were randomized to an initial strategy, randomization appeared to have little effect on what intervention was received.¹⁴⁵ In the methods section, Smith et al.¹⁴⁵ writes, “A successful screening trial of intrathecal morphine was required before implantable drug delivery system implant in patients not likely to benefit.” In the same publication in the results section, Smith et al.¹⁴⁵ also writes, “On the implantable drug delivery system arm, 22 patients (21.5%) did not have a pump implanted within the 4 weeks after randomization because of either adequate pain

relief, death, or other reasons.” Clinician interviews suggested that intrathecal pumps were considered only after all medical management options have been exhausted. This finding is congruent with the results presented by Smith et al.,¹⁴⁵ but at odds with the methods. Since no results related to a trial of intrathecal morphine were presented and all patients in the intrathecal pump arm that did not proceed to device implantation due to adequate pain relief or death, it was assumed that these 22 participants experienced at least 20% pain relief and had the same risk of mortality as their arm of randomization.

Poor reporting of trial outcomes by Smith et al.¹⁴⁵ inhibited the ability to use trial outcomes in the presumed intention-to-treat analysis – this publication does not actually describe the type of analysis. Smith et al.¹⁴³ also published an ‘as-treated’ analysis which provided sufficient detail on efficacy of treatments to generate transition probabilities for model parameters. It is unclear whether the use of this ‘as-treated’ analysis introduces bias into the model.

Costs for health states are all obtained from one study of 36 patients from the United States. Although this paper examined the same patient population as the model, generalizability of economic findings is unclear. Variations in practice patterns, resource availability, and remuneration may inhibit generalizability of economic findings to the Canadian context.

Overall, limited data regarding clinical effectiveness and costs was available, and the validity of available evidence is unclear. Future data collection that includes clinical endpoints, utility, and detailed cost data with the goal of informing economic evaluation could strengthen evidence-based resource allocation decisions in this context.

In the event that costs associated with health states are deemed unreasonable, an excel file is included in Appendix Q with the title “Neuromodulation Intrathecal Pump and Cancer.xlsm.” This copy of the model allows the user to input their own costs associated with health states, and will return immediate results. If the standard error is also known, the user is invited to enter both the mean and standard error, and the probabilistic sensitivity analysis can also be easily recreated.

24 Budget Impact Analysis: Spinal Cord Stimulation in BC

Summary:

- Budget impact prediction relies on the previously described SCS model in section 23.
- With an assumed annual incidence of SCS device insertion of 0.02/1,000 people, approximately 89.0 SCS devices will be inserted across BC each year.
- The cost to develop a multidisciplinary pain clinic, including fluoroscopy suite, is estimated to be \$2.0 million. However, less than half of the capacity of this pain clinic will be required to support neuromodulation. The development of multidisciplinary pain clinics will benefit patients beyond just those who may benefit from neuromodulation.
- In the scenario in which no new neuromodulation devices are implanted, expected costs over five years are \$19.5 million. Predicted costs to maintain the status quo in BC are \$22.1 million. This cost difference is likely due to initial device and implantation costs associated with SCS.
- In the scenario in which pain clinics without fluoroscopy suites are developed in the Northern Health region and Interior Health region to support neuromodulation, but all device management occurs at St. Paul's Complex Pain Program, expected costs over five years are \$44.7 million.
- In a strategy that develops pain clinics in the Northern Health region and Interior Health Region, and the existing pain clinic in Fraser Health region provides neuromodulation services, simple device insertions occur in-region and St. Paul's Complex Pain Program handles only the complex device insertions, expected costs over five years are \$46.1 million.

24.1 Purpose

To estimate the budget impacts of four possible implementation options over five years related to neuromodulation in BC, from the perspective of the Ministry of Health.

24.2 Methods

This budget impact analysis is informed by the SCS model described in this report, and predicts cost outcomes over five years for the options described in section 22. It is assumed that each option is initiated at the beginning of the fiscal year before any device implantations have occurred. All costs were converted to 2017 Canadian dollars with purchasing power parities and the consumer price index for all goods.^{138,147} SCS devices were assumed to have a lifetime of nine years.¹³⁹ as cited in 136

Insufficient data was available to develop models for all types of neuromodulation for all indications. This budget impact analysis uses the findings of the SCS model, described in section 23. Given that cost data underlying the SCS model is reflective of a Canadian setting and Canadian practice patterns, it is assumed that the costs per patient for SCS and CMM for failed back surgery are representative of the expected costs per patient for neuromodulation. Intrathecal

pump cost data were not collected in a Canadian setting, and it is unknown how generalizable economic findings are to the Canadian setting. Therefore, cost outcomes from the intrathecal pump model are not included in this analysis. Costs per patient for each year, resulting from the model in section 23, are presented in Table 34. These are predicted costs per year including the SCS implantation, all follow-up and routine care over time (more details are available in section 23).

Table 34. Expected costs per patient with SCS or CMM

	Expected Costs Per Patient (\$)				
	Year 1	Year 2	Year 3	Year 4	Year 5
SCS	\$35,263	\$11,518	\$11,433	\$11,349	\$11,265
CMM	\$14,738	\$14,629	\$14,521	\$14,414	\$14,308

Data gathered through key informant clinician interviews estimated that 22 SCS devices were implanted in the 2017/2018 year at St. Paul’s Complex Pain Program in the Vancouver Coastal Health Region (Table 23). In the same year, between 12 and 17 SCS devices were inserted in the Vancouver Island Health Authority; the midpoint of this range was assumed to reflect the total number of devices implanted (Table 23). Northern Health, Interior Health, and Fraser Valley Health all report referring patients to St. Paul’s Complex Pain Program, but the exact number of patients receiving devices from these health authorities is not known. In 2017/18, the Vancouver Island Health Authority served a population of 785,751 people and implanted approximately 14.5 SCS devices, or 0.02 devices per 1,000 people. Thus, this analysis assumes that SCS devices are inserted at this same rate in Northern Health, Interior Health, and Fraser Valley Health (Table 35). This leads to a predicted incidence of 89.0 SCS devices implanted per year in BC.

Table 35. Predicted number of SCS devices inserted by health region in BC

Health Region	Population Served (number of people)	Number of Devices Inserted in 2017-18	Predicted Number of Devices Inserted Annually
Vancouver Coastal Health	1,179,465	22.0	22.0
Vancouver Island Health Authority	785,751	14.5	14.5
Fraser Health	1,809,696	Unknown	33.4
Interior Health	749,853	Unknown	13.8
Northern Health	283,029	Unknown	5.2
Total:	4,807,794	Unknown	89.0

In option one; no new neuromodulation devices are funded by the province. An assumption was made that all eligible patients for spinal cord stimulation received the appropriate device. Thus, the 89.0 patients that would have received SCS in year 1 receive CMM with this option. It is also assumed that patients that had previously received SCS would continue to be supported.

Multidisciplinary pain clinics do not exist in Northern Health or Interior Health, and the existing multidisciplinary pain clinic in Fraser Health does not offer neuromodulation. Therefore, all eligible patients in those locations are assumed to be supported by CMM.

In option two, where the status quo is maintained, SCS continues to be funded at the current rate. The annual incidence of eligible patients in the province is consistent at 89.0 per year and it is assumed that all SCS devices inserted are implanted in Vancouver Coastal Health and Vancouver Island Health Authority. For patients eligible for SCS that do not receive the device in this option, it is assumed that they are managed in each health region with the CMM strategy. This means that 36.5 patients per year have SCS devices implanted in Vancouver Coastal Health and Vancouver Island Health Authority, and 52.5 receive CMM in Northern Health, Fraser Valley Health, and Interior Health.

Options three and four require the development of multidisciplinary pain clinics in regions that currently lack the capacity to adequately support patients whose pain is managed with neuromodulation. Consultation with key stakeholders identified that interdisciplinary pain clinics would need to be developed in the Northern and Interior regions. In these options, it is assumed that St. Paul's Complex Pain Program and the Nanaimo Regional Hospital Pain Program have

the required infrastructure to support these patients. Infrastructure requirements to optimally support neuromodulation were identified in key informant interviews with clinicians (section 18). This required infrastructure list was returned to experts in neuromodulation and the provincial pain management strategy in BC prior to inclusion in this analysis. Itemized costs associated with a multidisciplinary pain clinic capable of supporting neuromodulation patients is presented in Table 36. In each health region requiring the development of a multidisciplinary pain clinic, the assumption that space requirements could be accommodated within existing facilities was made. It was also assumed that multidisciplinary pain clinic annual costs do not include SCS patient treatment costs.

Table 36. Multidisciplinary pain program annual costs, and costs related to neuromodulation

Description ^[reference]	Annual Cost (2017 CAD)	Annual Cost Related to Neuromodulation (2017 CAD)
Fluoroscopy Suite for 3 days per month (equivalent annual cost over 5 years, calculated with discount rate of 1.5%) ¹⁴⁸	\$140,752.57	\$13,882.45
1 Neurosurgeon (half of time is required for neuromodulation) ¹⁴⁹	\$637,521.66	\$318,760.83
1 Anesthesiologist trained in neuromodulation trials and implantation (half of time is required for neuromodulation) ¹⁴⁹	\$410,304.46	\$205,152.23
1 Psychiatrist trained in neuromodulation trials and implantation (half of time is required for neuromodulation) ¹⁴⁹	\$248,062.01	\$124,031.01
3 Full-time equivalents of registered nurses (half of time is required for neuromodulation) ¹⁵⁰	\$202,410.72	\$101,205.36
1 Occupational Therapist or Physiotherapist for 3 days per month (average of the two	\$72,787.27	\$7,179.02

annual salaries is used) ^{151,152}		
1 Clinical Pharmacist (half of time is required for neuromodulation) ¹⁵³	\$91,630.72	\$45,815.36
1 Clinical Psychologist for 3 days per month ¹⁵⁴	\$95,911.64	\$9,459.78
1 Clinic Manager (half of time is required for neuromodulation) ¹⁵⁵	\$67,401.42	\$33,700.71
1 Social Worker (not specifically required for neuromodulation, but beneficial to any pain program) ¹⁵⁶	\$55,638.87	\$0
Subtotal not including fluoroscopy suite	\$1,881,668.77	\$845,304.30
Total including fluoroscopy suite	\$2,022,421.34	\$859,186.75

In option three, St. Paul's Complex Pain Program would be promoted as the quaternary center for neuromodulation in the province. It is assumed that existing infrastructure in St. Paul's is capable of absorbing the increased number of device implants without additional infrastructure costs. Multidisciplinary pain clinics would also be developed within Northern Health, and Interior Health for the purpose of referring patients to St. Paul's. The Fraser Health multidisciplinary pain clinic would be connected and aligned with the broader strategy. Under this option, all SCS devices are implanted at St. Paul's Complex Pain Program. Therefore, fluoroscopy suites are not required at the multidisciplinary pain clinics outside of St. Paul's Hospital.

In option four, multidisciplinary pain clinics are developed within Northern Health and Interior Health. The already established clinics would continue. Each multidisciplinary pain clinic requires the ability to implant SCS devices, therefore the total cost including a fluoroscopy suite is used. The cost of the fluoroscopy suite was calculated as the equivalent annual cost over five years and is therefore included in costs each year. With this options, all eligible patients receive SCS within each health region and no patients receive CMM. Assumed numbers of devices implanted in each health region is in Table 35.

24.3 Results

In option 1 no new neuromodulation implants are funded by the province. Patients that would have previously received neuromodulation implants instead receive medical management, and incur costs associated with a medical management strategy. This was the least costly option over five years, with a total cost of \$19.8 million (Table 37).

In the second option, in which the status quo is maintained, no new multidisciplinary pain clinics would be developed in regions that currently do not have the capacity to support neuromodulation. SCS devices would continue to be implanted and supported in Vancouver Coastal Health and Vancouver Island Health Authority, while other health regions in the province offer CMM. Over five years, the cost of this option is predicted to be \$22.1 million (Table 38).

The third option would require the development of multidisciplinary pain clinics in the Northern Health region and Interior Health region, each with a projected cost of \$1,881,669 (Table 39). It

is assumed that the multidisciplinary pain clinic in the Fraser Health region would be able to support neuromodulation patients without any additional costs. All 89.0 annual SCS device insertions would happen at St. Paul's Complex Pain Program. In addition, The first six months of care were assumed to be provided at St. Paul's. Thus, the total for the 89 cases is \$2,621,671 in year 1 (Table 39). The remainder of the follow-up was assumed to occur in each patient's home region (Table 39). The predicted five-year cost of this option across all health regions is \$44.7 million (Table 40).

In the fourth option, multidisciplinary pain clinics capable of device implantation would be developed in the Northern Health region and Interior Health region; this requires a multidisciplinary pain clinic equipped with a fluoroscopy suite equating to an annual cost of \$2,022,421. In addition, the implantation costs and patient costs of care would be borne by Northern and Interior for their respective patients, 5.2 for a cost of \$184,174 in year 1 and 13.8 for a cost of \$487,948 respectively (Table 41). Fraser Health would utilize an existing fluoroscopy suite while the programs for neuromodulation at VIHA and St. Paul's would continue to implant and care for their patients. St. Paul's Complex Pain Program would be the quaternary site in British Columbia for neuromodulation and deal with complex cases that could not be handled within each region. The predicted cost of this option is \$46.1 million over five years (Table 41). Table 42 presents a comparison of all four options.

Table 37. Implementation option one outcomes

Region	One-Year Outcomes			Five-Year Outcomes		
	Predicted SCS Patients (n)	Predicted CMM Patients (n)	Cost	Predicted SCS Patients (n)	Predicted CMM Patients (n)	Cost
Vancouver Coastal	0	22.0	\$324,232	0	110.0	\$4,815,938
VIHA	0	14.5	\$213,699	0	72.5	\$3,174,141
Fraser	0	33.4	\$492,178	0	167.0	\$7,310,497
Interior	0	13.8	\$203,935	0	69.2	\$3,029,126
Northern	0	5.2	\$76,975	0	26.1	\$1,143,332
Total	0	89.0	\$1,311,019	0	444.8	\$19,473,034

Table 38. Implementation option two outcomes

Region	One-Year Outcomes			Five-Year Outcomes		
	Predicted SCS Patients (n)	Predicted CMM Patients (n)	Cost	Predicted SCS Patients (n)	Predicted CMM Patients (n)	Cost
Vancouver Coastal	22	0	\$775,777	110	0	\$6,394,246
VIHA	14.5	0	\$511,308	72.5	0	\$4,214,389
Fraser	0	33.4	\$492,178	0	167	\$7,310,497
Interior	0	13.8	\$203,935	0	69.2	\$3,029,126
Northern	0	5.2	\$76,975	0	26.1	\$1,143,332
Total	36.5	52.5	\$2,060,173	182.5	262.3	\$22,091,591

Table 39. Implementation option three outcomes, one-year

Region	One-Year Outcomes					
	Predicted SCS Insertion Patients (n)	SCS Follow-Up in Region (n)	Infrastructure Costs for Pain Clinics	Device Insertion Costs	Follow-Up Costs	Total Costs
Vancouver Coastal	89.0	22	\$0	\$2,621,671	\$127,404	\$2,749,075
VIHA	0	14.5	\$0	\$0	\$83,971	\$83,971
Fraser	0	33.4	\$0	\$0	\$193,396	\$193,396
Interior	0	13.8	\$1,881,669	\$0	\$80,134	\$1,961,803
Northern	0	5.2	\$1,881,669	\$0	\$30,246	\$1,911,915
Total	89.0	89.0	\$3,763,338	\$2,621,671	\$515,151	\$6,900,159

*No patients eligible for SCS are treated with CMM in any region

Table 40. Implementation option three outcomes, five-year

Region	Five-Year Outcomes					
	Predicted SCS Insertion Patients (n)	SCS Follow-Up in Region (n)	Infrastructure Costs for Pain Clinics	Device Insertion Costs	Follow-Up Costs	Total Costs
Vancouver Coastal	444.8	110.0	\$0	\$13,108,357	\$3,152,377	\$16,260,733
VIHA	0	72.5	\$0	\$0	\$2,077,703	\$2,077,703
Fraser	0	167.0	\$0	\$0	\$4,785,245	\$4,785,245
Interior	0	69.2	\$9,408,344	\$0	\$1,982,781	\$11,391,124
Northern	0	26.1	\$9,408,344	\$0	\$748,393	\$10,156,736
Total	444.8	444.8	\$18,816,688	\$13,108,357	\$12,746,498	\$44,671,542

*No patients eligible for SCS are treated with CMM in any region

Table 41. Implementation option four outcomes

Region	One-Year Outcomes					Five-Year Outcomes				
	Predicted SCS Patients (n)	Predicted CMM Patients (n)	Infrastructure Costs for Pain Clinics	Patient Costs	Total Costs	Predicted SCS Patients (n)	Predicted CMM Patients (n)	Infrastructure Costs for Pain Clinics	Patient Costs	Total Costs
Vancouver Coastal	22.0	0	\$0	\$775,777	\$775,777	110.0	0	\$0	\$6,394,246	\$6,394,246
VIHA	14.5	0	\$0	\$511,308	\$511,308	72.5	0	\$0	\$4,214,389	\$4,214,389
Fraser	33.4	0	\$0	\$1,177,614	\$1,177,614	167.0	0	\$0	\$9,706,337	\$9,706,337
Interior	13.8	0	\$2,022,421	\$487,948	\$2,520,274	69.2	0	\$10,112,107	\$4,021,850	\$14,133,957
Northern	5.2	0	\$2,022,421	\$184,174	\$2,210,798	26.1	0	\$10,112,107	\$1,518,031	\$11,630,137
Total	89.0	0	\$4,044,843	\$3,136,822	\$7,181,665	444.8	0	\$20,224,214	\$25,854,854	\$46,079,068

Table 42. Costs for each implementation option by health region in BC

Region	Incident Eligible Patients Per Year (n)	Option 1 Cost: No new SCS implants funded		Option 2 Cost: Maintain the status quo		Option 3: All SCS implanted at St. Paul's Complex Pain Program		Option 4: A coordinated approach	
		1-Year	5-Year	1-Year	5-Year	1-Year	5-Year	1-Year	5-Year
Vancouver Coastal	22	\$0.3M	\$4.8M	\$0.8M	\$6.4M	\$3.1M	\$25.9M	\$0.8M	\$6.4M
VIHA	14.5	\$0.2M	\$3.2M	\$0.5M	\$4.2M	\$0	\$0	\$0.5M	\$4.2M
Fraser	33.4	\$0.5M	\$7.3M	\$0.5M	\$7.3M	\$0	\$0	\$1.2M	\$9.7M
Interior	13.8	\$0.2M	\$3.0M	\$0.2M	\$3.0M	\$1.9M	\$9.4M	\$2.5M	\$14.1M
Northern	5.2	\$0.08M	\$1.1M	\$0.08M	\$1.1M	\$1.9M	\$9.4M	\$2.2M	\$11.6M
Total:	89.0	\$1.3M	\$19.5M	\$2.1M	\$22.1M	\$6.9M	\$44.7M	\$7.2M	\$46.1M

***M = million

24.4 Conclusions

The least costly option over five years was option one, or to stop funding for SCS device implantation. The cost of this option was very similar to the costs of maintaining the status quo. However, the reduced cost for this option is misleading. After device implantation costs incurred during the first six months, costs of SCS are consistently lower than CMM. Beyond five years, the cost to the province to stop funding for SCS device implantation would be greater than to maintain the status quo. At steady state, the cost to provide CMM to 89.0 additional patients annually with a nine-year device lifetime is predicted to be \$11.5 million per year; and the cost to provide SCS to 89.0 patients is predicted to be \$11.1 million per year.

In options three and four, which required the development of additional multidisciplinary pain clinics in the Northern Health region and Interior Health region, costs were greater due to the development of multidisciplinary pain clinics. The costs of infrastructure requirements are fixed and would be incurred for equipment or to employ new staff, whether or not they were used entirely for neuromodulation. Consultation with expert clinicians suggested that less than half of the cost of each multidisciplinary pain clinic would be attributable to a neuromodulation program in option three or four.

Option four was the most expensive at \$46.1 million over five years. This is due to the development of two clinics with fluoroscopy suites, each of which incurs operating expenses of greater than \$2 million per year. Implanting all SCS devices at St. Paul's, which is described in option three, requires an investment of \$44.7 million over five years. This option relies on the existing expertise and infrastructure that already exists at St. Paul's Complex Pain Program.

This budget impact analysis attempts to link cost outcomes to implementation outcomes proposed in section 22. In addition to relying upon the assumptions made in the previously described SCS model for patients with failed back surgery syndrome, this analysis makes further assumptions. Data was not available to look at the eligible population for neuromodulation devices in BC, so it was assumed that there would be 89 incident patients per year eligible for SCS. However, it is known that Northern Health, Fraser Health, and Interior Health all refer their eligible patients to St. Paul's Complex Pain Program in Vancouver for neuromodulation care. This analysis may double count those patients and overestimate the size of the eligible

population. However, there may be eligible patients outside of Vancouver Coastal Health that would consider SCS if available closer to home.

In options three and four, it was assumed that the multidisciplinary pain clinic in the Fraser Health region was capable of providing care to patients with neuromodulation devices without additional costs. Nuanced data to understand precisely what capacity was present to support these patients in the Fraser Health region was not available. However, it is likely that additional resources would be required to develop this capacity in the Fraser Health region, and those costs were not captured in this analysis. To accommodate approximately 65 additional patients per year at St. Paul's under policy option three, further investment to increase capacity would likely be required. However, no data was available to quantify this assumption. Therefore, it was conservatively assumed that there would be no additional costs to increase capacity at St. Paul's. Options three and four likely underestimate costs to the healthcare system.

Although cost data from the study by Kumar and Rizvi¹³⁶, represented the perspective of a Canadian publicly funded healthcare system, it is known that the field of neuromodulation is quickly evolving. The cost data underlying this budget impact analysis is likely outdated. The analysis presented by Kumar and Rizvi¹³⁶ also suggests that the cost to provide SCS differs by the indication, and SCS use is not limited to failed back surgery syndrome in British Columbia. Data regarding the proportion of patients in British Columbia receiving SCS by the indication was not available.

To increase understanding of cost outcomes related to neuromodulation, it will be crucial to identify a cohort of eligible patients within administrative data. This analysis was hindered by a lack of data to identify patients that have received neuromodulation or could receive neuromodulation. Administrative data collected within BC includes cost outcomes, but without the capacity to identify patients that have received neuromodulation, the impact of neuromodulation on the publicly funded healthcare system in BC can only be estimated.

25 Conclusions

Systematic reviews of HTAs and RCT literature for the different types of neuromodulation in cancer and non-cancer pain resulted in mixed findings. Evidentiary support of high quality was found for clinical effectiveness and safety of SCS in certain non-cancer pain indications and intrathecal pumps in cancer pain. Intrathecal pumps, PNS, PNfS, and tSNS for non-cancer pain all returned very little low quality supportive evidence. SCS for cancer pain returned no evidence for review. Further research is needed to determine the clinical effectiveness and safety of intrathecal pumps, PNS, PNfS, and tSNS for chronic non-cancer pain management and SCS for chronic cancer pain management.

SCS is the most commonly employed neuromodulatory device across Canada and within BC. Four hospital-affiliated pain programs in BC provide neuromodulation for pain. Key informant patients and clinicians identified neuromodulation as highly effective and impactful in appropriate patients. The need for neuromodulation to be embedded within a greater pain program or strategy was emphasized.

Cost-utility analysis of SCS compared to CMM in FBSS patients indicated SCS is associated with higher QALYs at every time point. Device lifetime needs to be at least eight years in order for the two strategies to be cost-neutral, below SCS is more costly and above it is less costly. Cost-effectiveness analysis of intrathecal pumps compared to CMM in refractory cancer pain indicated intrathecal pumps resulted in greater life years at greater cost.

Four possible implementation scenarios were developed: (1) discontinue public funding for neuromodulation in BC; (2) maintain the status quo; (3) develop St. Paul's as the center for neuromodulation; and (4) develop a coordinated approach to neuromodulation across the five regional health authorities. The budget impact analysis of SCS in BC reported costs over five years of \$19.5 million, \$22.1 million, \$44.7 million, and \$46.1 million for each implementation scenario respectively. Each option has implementation and feasibility considerations that must be deliberated.

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Appendix A: Neuromodulation HTA Search

Neuromodulation HTA search

1. exp electric stimulation therapy/ or exp electric stimulation/ or exp deep brain stimulation/or exp infusion pumps, implantable/
2. (spinal cord stimulation or transcutaneous supraorbital nerve stimulation or peripheral nerve stimulation or peripheral nerve field stimulation or intrathecal pump or neuromodulation or electrical stimulation or neuromstimulation, or intrathecal drug administration or implantable infusion pump).mp
3. Exp pain/ or exp pain clinics/ or exp shoulder pain/ or exp pelvic pain/ or exp pain, postoperative/ or exp pain measurement/ or exp neck pain/ or exp chest pain/
4. (pain or pain management or cancer pain or non-cancer pain or chronic pain or intractable pain).mp
5. 1 or 2
6. 3 or 4
7. 5 and 6

Appendix B: Search Strategy for SCS in Cancer Patients

SCS, Cancer inception-current, RCTS only

1. exp electric stimulation therapy/ or exp electric stimulation/ or exp spinal cord stimulation/
2. (spinal cord stimulation or neuromodulation or electrical stimulation or neuromstimulation).tw,kw
3. Exp pain/ or exp pain management/ or exp cancer pain/ or exp chronic pain or exp pain clinics/
4. (pain or pain management or cancer pain or chronic pain or intractable pain).tw,kw
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. clinical trials as topic.sh.
13. randomly.ab.
14. trial.ti.
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp animals/ not humans.sh.
17. 15 not 16
18. 7 and 17

CINAHL

1. TI (“electric stimulation therap*” or “electric stimulat*” or “spinal cord stimulat*” or “neuromodulat*” or “neuromstimulat*”) or AB (“electric stimulation therap*” or “electric stimulat*” or “spinal cord stimulat* or neuromodulat*” or “neuromstimulat*”)
2. TI (“pain” or “pain management” or “cancer pain” or “chronic pain” or “pain clinic” or “intractable pain”) or AB (“pain” or “pain management” or “cancer pain” or “chronic pain” or “pain clinic” or “intractable pain”)
3. 1 and 2

Appendix C: Search Strategy for SCS in Non-Cancer Patients

SCS, 2013-current, RCTs non-cancer

MEDLINE; EMBASE

1. exp electric stimulation therapy/ or exp electric stimulation/ or exp spinal cord stimulation/
2. (spinal cord stimulation or neuromodulation or electrical stimulation or neuromstimulation).tw,kw
3. Exp pain/ or exp pain management/ or exp chronic pain or exp pain clinics/ or exp shoulder pain/ or exp pelvic pain/ or exp pain, referred or exp pain, postoperative/ or exp pain measurement/ or exp neck pain/ or exp musculoskeletal pain/ or exp chest pain/ or exp breakthrough pain/
4. (pain or pain management or non-cancer pain or chronic pain or intractable pain).tw,kw
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. limit 7 to yr="2013 -Current"
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. clinical trials as topic.sh.
14. randomly.ab.
15. trial.ti.
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp animals/ not humans.sh.
18. 16 not 17
19. 8 and 18

CINAHL

1. TI (“electric stimulation therap*” or “electric stimulat*” or “spinal cord stimulat*” or “neuromodulat*” or “neuromstimulat*”) or AB (“electric stimulation therap*” or “electric stimulat*” or “spinal cord stimulat*” or “neuromodulat*” or “neuromstimulat*”)

2. TI (“pain” or “pain management” or “chronic pain” or “pain clinic” or “shoulder pain” or “pelvic pain” or “referred pain” or “postoperative pain” or “pain measurement” or “neck pain” or “musculoskeletal pain” or “chest pain” or “breakthrough pain” or “intractable pain”) or AB (“pain” or “pain management” or “chronic pain” or “cancer pain” or “pain clinic” or “shoulder pain” or “pelvic pain” or “referred pain” or “postoperative pain” or “pain measurement” or “neck pain” or “musculoskeletal pain” or “chest pain” or “breakthrough pain” or “intractable pain”)

3. 1 and 2

Limited Jan 2013-current

Appendix D: SCS Non-Cancer Included Study Characteristics

Table 1. SCS Non-cancer Pain Included Study Characteristics

Author, trial (if applicable), country, year	Technology details	Intervention	Patient Characteristics	Primary outcome	Any secondary outcome(s)	Quality assessment
Al-Kaisy, SCS Frequency Study, UK, 2017	Spinal cord stimulation Sponsored by Medtronic, Inc.; all subjects implanted with dual octapolar leads; rostral tip of the implanted epidural leads located approximately between the vertebral body of T7 and T10	Four settings: sham, 1200 Hz at 180 µsec, 3030 Hz at 60 µsec, and 5882 Hz at 30 µsec, each tested for three weeks in a random order	Inclusion criteria: diagnosed with failed back surgery syndrome; at least 18 years of age; VAS score ≥ 6; on stable pain relief medication Type of pain: failed back surgery syndrome n=24 Mean age (SD): 47.9 % male: 66.7%	VAS score (SD) <ul style="list-style-type: none"> Baseline: 7.75 (1.13) Sham: 4.83 (2.45) 1200 Hz: 4.51 (1.87) 3030 Hz: 4.57 (2.09) 5882 Hz: 3.22 (1.98), p=.002 	Subjects who felt stimulation sensation (% saying no) <ul style="list-style-type: none"> Sham: 83.3% 1200 Hz: 62.5% 3030 Hz: 75% 5882 Hz: 87.5% 	Low
deJongste, the Netherlands, 1994	Permanent implanted pulse generator	No SCS vs. SCS	Inclusion criteria: intractable angina; pharmacologically optimal drug treatment for at least 1 month Type of pain: refractory angina n=17 Mean age (SD): 63.2	Mean exercise duration in seconds (SE) <ul style="list-style-type: none"> Control: 694 (67) Intervention: 827 (138), p<0.05 Significant difference between change in SCS 	None reported	High

			<p>(3.6) in control, 62.3% (2.6) in intervention</p> <p>% male: 88.9% in control, 87.5% in intervention</p>	<p>group vs change in control group, $p < 0.03$</p> <p>HRQOL</p> <ul style="list-style-type: none"> Control: 1.25 (1.10-1.71) Intervention: 2.06 (1.65-2.26), $p < .05$ 		
De Ridder, Belgium, 2013	Spinal cord stimulation: Patients underwent implantation of a lamitrode via laminectomy	Three modes: burst, tonic (40 or 50 Hz), placebo	<p>Inclusion criteria: patients are medically intractable to opioids and antiepileptic drugs</p> <p>Type of pain: failed back surgery syndrome, myelomalacia</p> <p>n=15</p> <p>Mean age (SD): 54.07</p> <p>% male: 26.7%</p>	<p>VAS scores (raw improvement, % change)</p> <p>Back pain</p> <ul style="list-style-type: none"> Placebo: 1.4, 18.9% Tonic: 2.2, 30.3% Burst: 3.8, 51.3% $p < .01$ <p>Limb pain</p> <ul style="list-style-type: none"> Placebo: 0.9, 11.7% Tonic: 3.9, 51.5% Burst: 3.9, 52.7% $p < .05$ <p>General pain</p> <ul style="list-style-type: none"> Placebo: 0.9, 10.9% Tonic: 2.5, 	<p>PVAQ scores (raw improvement, % change)</p> <p>Attention to pain</p> <ul style="list-style-type: none"> Placebo: 0.5, 3.3% Tonic: 0.8, 5.0% Burst: 1.2, 7.6% $p < .05$ <p>Attention to changes in pain</p> <ul style="list-style-type: none"> Placebo: 0.6, 3.2% Tonic: 0.7, 3.9% Burst: 1.9, 10.0% $p < .05$ 	Some concerns

				<ul style="list-style-type: none"> 30.9% Burst: 4.5, 55.0% p<.01 		
de Vos, the Netherlands, 2014	SCS; one electrode lead was implanted in the epidural space and positioned where the patient reported optimal overlap between paresthesia and the painful area, with the tip of the electrode lead between vertebral level T9 and T12; an implantable pulse generator was implanted subcutaneously in either the anterior abdominal wall or the upper buttock and connected to the electrode lead	Patients randomized to receive either SCS + conventional medical practice or treatment as usual (control) without SCS	<p>Inclusion criteria: at least 18 years old; had tried all conventional pain treatments; average VAS score of at least 50</p> <p>Type of pain: refractory diabetic neuropathy</p> <p>n=60</p> <p>Mean age (SD): 58 (11)</p> <p>% male: 63%</p>	<p>Patients with more than 50% pain reduction (assessed with the VAS)</p> <ul style="list-style-type: none"> Control: 1 (5%) Intervention: 25 (60%), p<.001 	<p>Quality of life, average (SD) (MPQ QoL score)</p> <ul style="list-style-type: none"> Control: 14 (6) Intervention: 8 (7), p<.001 	Low
Duarte, UK, 2015	SCS; no other details provided	Conventional medical practice (CMP; control) vs. SCS + CMP	<p>Inclusion criteria: 18 years or older; VASPI score of at least 50</p> <p>Type of pain: refractory diabetic neuropathy</p> <p>n=60</p> <p>Mean age (SD): 59 (11)</p> <p>% male: 63%</p>	<p>VASPI score</p> <ul style="list-style-type: none"> Control: 66 (22) Intervention: 29 (27), p<.001 <p>QoL (EQ-5D score, adjusted for baseline score)</p> <ul style="list-style-type: none"> Control: 0.178 Intervention: 0.258, p<.001 	None reported	Some concerns
Hautvast, the Netherlands, 1998	Permanent, subcutaneously implanted bipolar pulse generator	Inactive SCS device vs. active SCS	<p>Inclusion criteria: chronic intractable angina pectoris class III or IV despite medication; ineligible</p>	<p>Exercise capacity, time to angina at follow-up (seconds) (SD)</p> <ul style="list-style-type: none"> Control: 246 	<p>Mean VAS score at follow-up (SD)</p> <ul style="list-style-type: none"> Control: 3.2 (1.4) Intervention: 	Some concerns

			<p>for coronary angioplasty or artery bypass grafting</p> <p>Type of pain: refractory angina</p> <p>n=25</p> <p>Mean age (SD): 63 (7) in control, 62 (8)</p> <p>% male: 66.7% in control, 46.2% in intervention</p>	<p>(97)</p> <ul style="list-style-type: none"> Intervention: 319 (85), p=.01 	<p>2.6 (1.4), not significant</p>	
Jivegard, Sweden, 1995	Permanent implant implanted percutaneously	Peroral analgesic treatment prescribed as required by the patient (control) vs. SCS	<p>Inclusion criteria: severe chronic lower limb ischemia; arteriosclerotic and diabetic patients; rest pain and/or ischemic ulcerations for more than 2 weeks</p> <p>Type of pain: critical limb ischemia</p> <p>n=51</p> <p>Mean age (SD): 73 (12)</p> <p>% male: 54% in control, 56% in intervention</p>	<p>Limb salvage rates at 18 months</p> <ul style="list-style-type: none"> Control: 45% Intervention: 62%, not significant 	<p>Significant long-term pain relief at 18-month follow-up (assessed with VAS)</p> <ul style="list-style-type: none"> Control: too few observations Intervention: p<.01 	Low
Kriek, the Netherlands, 2016	SCS; single 8 contact Octrode™ lead to cover the painful area and Eon™ rechargeable internal pulse	Five conditions: 40- (standard), 500-, and 1200-Hz stimulation,	<p>Inclusion criteria: confirmed CRPS diagnosis in one extremity; therapy</p>	<p>VAS score, mean (SE, 95% CI)</p> <ul style="list-style-type: none"> Standard: 39.83 (4.7, 	None reported	Low

	generator	burst, and sham (placebo)	<p>resistant with a VAS score >5; indication for SCS in accordance with Dutch national guidelines</p> <p>Type of pain: complex regional pain syndrome</p> <p>n=29</p> <p>Mean age (SD): 42.55 (12.83)</p> <p>% male: 13.8%</p>	<p>30.19-49.47)</p> <ul style="list-style-type: none"> • 500 Hz: 40.13 (4.94, 30.02-50.24) • 1200 Hz: 42.89 (4.79, 33.09-52.70) • Burst: 47.98 (5.26, 37.22-58.75) • Placebo: 63.74 (3.51, 56.56-70.91), p<.001 <p>MPQ average pain score, mean (SE, 95% CI)</p> <ul style="list-style-type: none"> • Standard: 4.70 (0.40, 3.89-5.50) • 500 Hz: 5.10 (0.45, 4.18-6.03) • 1200 Hz: 5.31 (0.46, 4.36-6.26) • Burst: 5.66 (0.49, 4.65-6.66) • Placebo: 7.07 (0.28, 6.50-7.63), p<.001 <p>GPE score, mean (SE, 95% CI)</p>		
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				<p>Satisfaction</p> <ul style="list-style-type: none"> • Standard: 5.28 (0.29, 4.69-5.86) • 500 Hz: 5.31 (0.27, 4.76-5.86) • 1200 Hz: 4.97 (0.26, 4.43-5.50) • Burst: 4.72 (0.34, 4.02-5.43) • Placebo: 3.52 (0.35, 2.79-4.24), p<.001 <p>Improvement</p> <ul style="list-style-type: none"> • Standard: 4.93 (0.20, 4.53-5.34) • 500 Hz: 5.00 (0.23, 4.53-5.47) • 1200 Hz: 4.72 (0.21, 4.29-5.15) • Burst: 4.55 (0.24, 4.06-5.05) • Placebo: 3.79 (0.27, 3.24-4.34), p=.004 		
Kumar, Canada, PROCESS Trial, 2007	Implantable neurostimulation system	CMM vs. SCS + CMM	Inclusion criteria: neuropathic pain of radicular origin	Patients achieving at least 50% relief (assessed with	Mean VAS score, back pain (SD) <ul style="list-style-type: none"> • Control: 51.6 	High

			<p>predominantly in the legs; VAS ≥ 50; documented history of nerve injury; pain for at least 6 months</p> <p>Type of pain: FBSS</p> <p>n=100</p> <p>Mean age (SD): 52 (10.7) in control, 48.9 (10) in intervention</p> <p>% male: 44% in control, 58% in intervention</p>	<p>VAS)</p> <ul style="list-style-type: none"> Control: 9% Intervention: 48%, p<.001 	<p>(26.7)</p> <ul style="list-style-type: none"> Intervention: 40.6 (24.9), p=.008 <p>Mean VAS score, leg pain</p> <ul style="list-style-type: none"> Control: 66.6 (24.0) Intervention: 39.9 (26.3), p<.001 <p>Satisfied with pain relief</p> <ul style="list-style-type: none"> Control: 18% Intervention: 66%, p<.001 <p>Mean Oswestry Disability Index (ODI) score (SD)</p> <ul style="list-style-type: none"> Control: 56.1 (17.9) Intervention: 44.9 (18.8), p=.0002 	
Lanza, the SCS-ITA trial, Italy, 2011	SCS devices implanted	Paresthetic SCS (PS) vs. subliminal SCS (SS) vs. sham SCS (NS, control)	Inclusion criteria: stable angina for at least two months; documented obstructive coronary artery disease and/or documented previous acute myocardial infarction; reversible myocardial ischemia;	<p>Number of angina episodes at 1 month, median (range)</p> <ul style="list-style-type: none"> NS/control: 20 (2-27) SS: 7 (0-15) PS: 2 (0-94) Significant 	<p>Mean VAS score (SD)</p> <ul style="list-style-type: none"> NS/control: 45.0 (14) SS: 49.6 (14) PS: 67.0 (17) 	High

			<p>unsuitable for surgical and percutaneous coronary artery revascularization</p> <p>Type of pain: refractory angina pectoris</p> <p>n=25 (8 in NS, 7 in SS, 10 in PS)</p> <p>Mean age (SD): 70.5 (12) in NS, 66.0 (11) in SS, 67.5 (13) in PS</p> <p>% male: 75% in NS, 86% in SS, 70% in PS</p>	<p>difference between PS and NS</p>		
North, US, 2005	Placement of a temporary percutaneous electrode, after which patients received permanent placement if pain improved	CMM vs. SCS + CMM	<p>Inclusion criteria: surgically remediable nerve root compression; complaints of persistent or recurrent radicular pain; previous therapy</p> <p>Type of pain: FBSS</p> <p>n=60</p> <p>Mean age (SD): ranged from 26-76 years</p> <p>% male: 50%</p>	<p>At least 50% pain relief</p> <ul style="list-style-type: none"> Control: 12% Intervention: 47%, p=.01 	<p>Opioid use stable or decreased</p> <ul style="list-style-type: none"> Control: 58% Intervention: 87%, p=.025 No significant difference in pain related to activities in daily living between groups 	High
Perruchoud, Switzerland, 2012	Medtronic SCS system	Two conditions: sham and high frequency SCS	<p>Inclusion criteria: currently be treated with SCS for chronic pain; have stable pain control;</p>	<p>PGIC</p> <ul style="list-style-type: none"> Patients responding to sham: 30.3% 	<p>VAS score</p> <ul style="list-style-type: none"> Sham: 4.26 HFSCS: 4.35, p=.82 	Low

			<p>be implanted with a Medtronic generator</p> <p>Type of pain: chronic low back pain radiating in one or both legs</p> <p>n=33</p> <p>Mean age (SD): 54.2 (10.7)</p> <p>% male: 48.5%</p>	<ul style="list-style-type: none"> Patients responding to HFSCS: 42.4% 	<p>EQ-5D index</p> <ul style="list-style-type: none"> Sham: 0.463 HFSCS: 0.480, p=.78 	
Schu, Germany, 2013	St. Jude Medical SCS system	<p>Three conditions: tonic stimulation at 500 Hz; burst stimulation (five pulses, 500 Hz each, 40 times per second); placebo</p>	<p>Inclusion criteria: 18-75 years; diagnosis of FBSS; had an implanted SCS system at least three months previously; receiving conventional tonic stimulation</p> <p>Type of pain: FBSS</p> <p>n=20</p> <p>Mean age (SD): 58.6 (10.2)</p> <p>% male: 35%</p>	<p>NRS score, mean (SD) (higher score = more painful)</p> <ul style="list-style-type: none"> Baseline conventional: 5.6 (1.7) Tonic: 7.1 (1.9) Burst: 4.7 (2.5), p<.05 Placebo: 8.3 (1.1) 	<p>Mean pain quality scores (using Short Form MPQ), mean (SD)</p> <ul style="list-style-type: none"> Baseline conventional: 25.0 (7.1) Tonic: 28.6 (10.2) Burst: 19.5 (10.5), p<.05 Placebo: 33.5 (11.8) <p>Mean pain-related disability scores, using Oswestry Disability Index (ODI), mean (SD)</p> <ul style="list-style-type: none"> Baseline conventional: 22.3 (8.0) Tonic: 24.6 	Low

					(7.3) <ul style="list-style-type: none"> Burst: 19.2 (8.0) Placebo: 29.5 (10.3) 	
Slangen, the Netherlands, 2014	SCS octapolar lead (Synergy Versitrel or PrimeAdvanced; Medtronic)	Best medical conditions (BMT; control) vs. SCS + BMT	Inclusion criteria: 18-80 years; moderate to severe painful diabetic peripheral neuropathy present in the lower limbs; insufficient pain relief and/or unacceptable side effects; pain present for more than 12 months; NRS score ≥ 5 Type of pain: diabetic peripheral neuropathy n=36 Mean age (SD): 56.5 (8.0) in control, 57.1 (12.4) in intervention % male: 64% in control, 68% in intervention	Treatment success <ul style="list-style-type: none"> Control: 1/14 (17%) Intervention: 13/22 (59%), p<.009 Change in NRS score <ul style="list-style-type: none"> Control: no change Intervention: - 3.1 points, p<.001 	None reported	Low
Spincemaille, ESES trial, the Netherlands, 2000	Permanent implant implanted subcutaneously	CMM vs. SCS + CMM	Inclusion criteria: surgically non-constructible atherosclerotic vessel disease in one lower limb; persistent pain for at least two weeks; being treated with analgesics;	Limb salvage rates at 2 years <ul style="list-style-type: none"> Control: 46% Intervention: 52%, not significant Mean VAS score	None reported	Low

			<p>Type of pain: critical limb ischemia</p> <p>n=120</p> <p>Mean age (SD): 72 (10.6) in control, 73 (9.8) in intervention</p> <p>% male: 62% in control, 55% in intervention</p>	<p>at 18 months (SE)</p> <ul style="list-style-type: none"> Control: 25.2 (5) Intervention: 22.5, not significant <p>Mean McGill score at 18 months</p> <ul style="list-style-type: none"> Control: 8.1 Intervention: 8.7, not significant 		
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Appendix E: SCS Non-Cancer Risk of Bias Assessment

Table 1. SCS Non-cancer Pain RCT Risk of Bias Assessment

Study	Bias arising from randomization	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Final bias assessment
Al-Kaisy	Low	Low	Low	Low	Low	Low
De Jongste	Some concerns	Some concerns	Low	High	Some concerns	High
De Ridder	Some concerns	Low	Low	Low	Low	Some concerns
De Vos	Low	Low	Low	Low	Low	Low
Duarte	Some concerns	Low	Low	Low	Low	Some concerns
Hautvast	Some concerns	Some concerns	Low	Low	Low	Some concerns
Jivegard	Low	Low	Low	Low	Low	Low
Kriek	Low	Low	Low	Low	Low	Low
Kumar	Low	Low	High	High	Low	High
Lanza	Some concerns	Some concerns	High	High	Low	High
North	Low	Low	Low	High	Low	High
Perruchoud	Low	Low	Low	Low	Low	Low
Schu	Low	Low	Low	Low	Low	Low
Slangen	Low	Low	Low	Low	Low	Low
Spincemaille	Low	Low	Low	Low	Low	Low

Appendix F: Search Strategy for PNfS in Non-Cancer Patients

PNfS, 2012-current, RCTs, Non cancer

MEDLINE; EMBASE

1. exp electric stimulation therapy/ or exp electric stimulation/
2. (peripheral nerve stimulation or peripheral nerve field stimulation or pfns or neuromodulation or electrical stimulation or neuromstimulation).tw,kw
3. Exp pain/ or exp pain management/ or exp chronic pain or exp pain clinics/ or exp shoulder pain/ or exp pelvic pain/ or exp pain, referred or exp pain, postoperative/ or exp pain measurement/ or exp neck pain/ or exp musculoskeletal pain/ or exp chest pain/ or exp breakthrough pain/
4. (pain or pain management or non-cancer pain or chronic pain or intractable pain).tw,kw
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. limit 7 to yr="2012 -Current"
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. clinical trials as topic.sh.
14. randomly.ab.
15. trial.ti.
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp animals/ not humans.sh.
18. 16 not 17
19. 18 and 8

CINAHL

1. TI ("peripheral nerve stimulation" or "peripheral nerve field stimulation" or "pfns" or "neuromodulation" or "neurostimulation") or AB ("peripheral nerve stimulation" or "peripheral nerve field stimulation" or "pfns" or "neuromodulation" or "neurostimulation")

2. TI (“pain” or “pain management” or “chronic pain” or “pain clinic” or “shoulder pain” or “pelvic pain” or “referred pain” or “postoperative pain” or “pain measurement” or “neck pain” or “musculoskeletal pain” or “chest pain” or “breakthrough pain” or “intractable pain”) or AB (“pain” or “pain management” or “chronic pain” or “cancer pain” or “pain clinic” or “shoulder pain” or “pelvic pain” or “referred pain” or “postoperative pain” or “pain measurement” or “neck pain” or “musculoskeletal pain” or “chest pain” or “breakthrough pain” or “intractable pain”)

3. 1 and 2

Appendix G: PNS Non-Cancer Included Study Characteristics

Table 1. PNS Non-cancer Pain Included Study Characteristics

Author, trial (if known), country, year	Technology details	Intervention	Patient Characteristics	Primary outcome	Any secondary outcome(s)
<p>Silberstein et al., US, 2012</p> <p>Subsequent publications from the same trial (see secondary outcomes column for additional reported outcomes):</p> <p>Dodick et al., US, 2015</p> <p>Mekhail et al., US, 2017</p> <p>Sharan et al.</p>	<p>PNS: percutaneous quadripolar leads (Quattrode, St. Jude Medical, Plano, TX, USA) and The Genesis (St. Jude Medical) non-rechargeable implantable pulse Generator (IPG).</p>	<p>Active vs. sham stimulation</p>	<p>Inclusion criteria: met diagnostic criteria for chronic migraine headache; refractory to ≥ 2 migraine-specific acute medications; refractory to ≥ 2 classes of prophylactic medications; VAS of ≥ 6cm (on 10cm line); posterior head pain or pain originating in the cervical region.</p> <p>Type of pain: Chronic migraine</p> <p>N = 157</p> <p>Mean age: 44.6 (± 1.03) for control group; 45.0 (± 11.3) for active group</p> <p>% male: 9 (17.3%) in control group; 24 (22.9%) in active group</p>	<p>Pain relief (VAS scores) – achieved 50% reduction in pain from baseline</p> <ul style="list-style-type: none"> 18 patients (17.1%) of the active group vs. 7 patients (13.5%) of sham group (not significant difference, 95% lower confidence bound of -0.06; p=0.55). 	<p>Dodick et al. 2015: Headache days reduction from baseline</p> <ul style="list-style-type: none"> ITT patients: reduced by 6.7 (± 8.4) days, (p<0.001) Control (ICM): reduced by 7.7 (± 8.7) <p>Patient disability (MIDAS score) – reduction from baseline</p> <ul style="list-style-type: none"> ITT: reduced by 50.9 (± 71.9) points Control (ICM): reduced by 57.9 (± 71.8) points <p>Sharan et al. 2015 Adverse events (AEs) after 52 weeks</p> <ul style="list-style-type: none"> 221 AEs in 111/157 patients (71%) <p>Incidence rate of additional surgeries</p>

2015					<p>performed to resolve AEs:</p> <ul style="list-style-type: none"> • For a surgeon's first 5 implants: 64/72 (88.9%) • Surgeons with 6-10 prior implants experience: 19/49 (38.8%) • Surgeons with >10 prior implants experience: 10/36 (27.8%) <p>Device/Procedure-related AEs subsequent to PNS implants</p> <ul style="list-style-type: none"> • For surgeons with ≤5 prior implants: 63/84 • For surgeons with 6-10 prior implants: 12/84 <p>For surgeons with >10 prior implants: 9/84</p>
Plazier et al., Belgium, 2014. [#1132]	ONS: eight-contact trial wire (Octrode lead; St. Jude Medical) and external multi-trial stimulator (St. Jude Medical) pre-programmed with five stimulation frequencies (6,	Effective stimulation vs. placebo	<p>Inclusion criteria: suffering from fibromyalgia; intractable to tricyclic antidepressants (amitryptiline), pain medication, magnesium supplements, physical therapy, and psychological support.</p> <p>Type of pain: fibromyalgia (musculoskeletal pain)</p>	<p>Pain intensity (VAS)</p> <ul style="list-style-type: none"> • Baseline: 8.64 (±1.36) • Effective group, after 5 weeks: 5.20 (±1.24) • Placebo group after 5 weeks: 6.93 (±1.80) 	<p>Pain catastrophizing scale</p> <ul style="list-style-type: none"> • Baseline: 20.55 (±8.83) • Effective group after 5 weeks: 13.20 (±7.94) • Placebo group after 5 weeks: 17.62 (±9.05)

	10, 12, 18, and 40 Hz).		<p>N = 11</p> <p>Mean age: 42.45 years (\pm8.31)</p> <p>% male: 0 (0%)</p>		
Plazier et al., Belgium, 2015 [#1133]	ONS (C2 Nerve Field Stimulation): sub-electrode (Octrode, St. Jude Medical) and external trial pulse generator (Multi-program Trial System, St. Jude Medical).	“Minimal stimulation” (0.1mA); “sub-threshold stimulation”; “Supra-threshold stimulation”	<p>Inclusion criteria: chronic widespread pain \geq 3 months in all 4 body quadrants; failed \geq 3 documented medically supervised treatments.</p> <p>Type of pain: fibromyalgia (musculoskeletal pain)</p> <p>N = 40</p> <p>Mean age: not provided</p> <p>% male: not provided</p>	<p>FIQ (Fibromyalgia Impact Questionnaire) scores</p> <ul style="list-style-type: none"> • Baseline: 65.66 • Minimal: 53.87 • Sub-threshold: 51.21 • Supra-threshold: 42.09 ($p < .001$) 	Pain Vigilance and Awareness Questionnaire (PVAQ); Pain Catastrophizing Scale (PCS); Tender Point Examination (TPE); and Numeric Rating Scale (NRS).
Schoenen et al., Belgium, 2013. [#1243]	PNS; using ATI SPG neuro-stimulator.	Full stimulation; sub-perception stimulation; sham stimulation.	<p>Inclusion criteria: 18-65 years; diagnosed with chronic cluster headaches (CCH); minimum of 4 CHs/week.</p> <p>Type of pain: chronic cluster headaches (CCH)</p> <p>N = 32</p> <p>Mean age: 45 years</p> <p>% male: 84%</p>	<p>Pain relief and pain freedom, at 15 minutes of therapy</p> <ul style="list-style-type: none"> • Full-stimulation: 67.1% achieved pain relief; 34.1% achieved pain freedom ($p < 0.0001$). • Sham-stimulation: 7.4% achieved pain relief; 1.5% achieved pain freedom ($p < 0.0001$). 	
Slotty et al., Germany,	ONS (PNS), using bilateral	Effective stimulation	Inclusion criteria: fulfilled IHS criteria for chronic	VAS Scores after treatment	MPQ scores: <ul style="list-style-type: none"> • Group 1: 8.37 (\pm3.70)

2015 [#1312]	ONS lead implantation	(group 1), sub-threshold stimulation (group 2), and no stimulation (group 3)	migraine Type of pain: chronic migraine N = 8 Mean age: not available % male: not available	<ul style="list-style-type: none"> • Group 1: 1.98 (±1.56) • Group 2: 5.65 (±2.11) • Group 3: 8.45 (±0.99) 	<ul style="list-style-type: none"> • Group 2: 17.38 (±3.42) • Group 3: 26.04 (±4.66)
Saper et al., US, 2011	ONS (Medtronic 7427 Synergy and 7427 V Synergy Versitrel IPGs).	“Adjustable stimulation” (AS), “preset stimulation” (PS), “medical management/control” (MM) and “ancillary group”	Inclusion criteria: fulfilled 2004 IHS criteria for chronic migraine headache Type of pain: chronic migraine N = 75 Mean age: 43 (±10.6) years % male: 13 (20%)	Reduction in headache days per month (from baseline) <ul style="list-style-type: none"> • AS: 6.7(±10.0) days, 27.0 (±44.8)% • PS: 1.5 (±4.6) days, 8.8 (±28.6)% • MM: 1.0 (±4.2) days, 4.4 (±19.1)% • Ancillary group: 9.1 (±12.3) days, 39.9 (±51.0)% 	Reduction in overall pain intensity <ul style="list-style-type: none"> • AS: 1.5(±1.6) • PS: 0.5 (±1.3) • MM: 0.6 (±1.0) • Ancillary group: 1.9 (±3.5) days, 39.9 (±51.0)%

Appendix H: PNfS Non-Cancer Included Study Characteristics

Table 1. PNfS Non-cancer Pain Included Study Characteristics

Author, trial (if known), country, year	Technology details	Intervention	Patient Characteristics	Primary outcome	Any secondary outcome(s)
Eldabe et al., SubQStim study, UK, 2018 [#430]	Subcutaneous Nerve Stimulation (SQS)	SQS plus optimal medical management (SQS+OMM) vs. optimal medical management (OMM)	<p>Inclusion criteria: diagnosed with failed back surgery syndrome (FBSS); aged 18 or older</p> <p>Type of pain: back pain due to failed back surgery syndrome</p> <p>N = 116</p> <p>Mean age = 51.6 (\pm11.1) years</p> <p>% male: 50 (43.1%)</p>	<p>Pain reduction (\geq50%) 9 months from baseline</p> <ul style="list-style-type: none"> • SQS+OMM: 19 patients (33.9%) achieved \geq50% pain reduction • OMM: 1 patient (1.9%) achieved \geq50% pain reduction • $p < 0.0001$ 	<p>Pain reduction (\geq50%) 6 months from baseline</p> <ul style="list-style-type: none"> • SQS+OMM: 15 patients (26.8%) • OMM: 1 patient (1.7%) <p>Pain reduction (\geq30%) 9 months from baseline</p> <ul style="list-style-type: none"> • SQS+OMM: 25 patients (44.6%) • OMM: 3 patients (5.0%)

Appendix I: PNS Non-Cancer Risk of Bias Assessment

Table 1. PNS Non-cancer Pain Included Study Risk of Bias Assessment

Study	Bias arising from randomization	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Final bias assessment
Dodick et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mekhail et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sharan et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Silberstein et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Plazier et al.	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Plazier et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Schoenen et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Slotty et al.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Saper	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Appendix J: PNfS Non-Cancer Risk of Bias Assessment

Table 1. PNfS Non-cancer Pain Included Study Risk of Bias Assessment

Study	Bias arising from randomization	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Final bias assessment
Eldabe et al.	Low risk	Some concerns	Some concerns	Some concerns	Low risk	Some concerns

Appendix K: Search Strategy for Supraorbital TENS

Supraorbital, 2015-current, all study designs

MEDLINE; EMBASE

1. (transcutaneous supraorbital nerve stimulation or supraorbital nerve stimulation or supraorbital or supraorbital stimulation or supraorbital neurostimulation or t-SNS or SNS).tw,kw.
2. Exp pain/ or exp pain management/ or exp chronic pain or exp pain clinics/ or exp pain measurement/ or exp migraine disorders/
3. (pain or pain management or non-cancer pain or chronic pain or intractable pain or migraine).tw,kw
4. 2 or 3
5. 1 and 4
6. limit 5 to yr="2015 -Current"

CINAHL

1. TI ("transcutaneous supraorbital nerve stimulat*" or "supraorbital stimulation" or "supraorbital neurostimulat*" or "t-SNS" or "SNS") or AB ("transcutaneous supraorbital nerve stimulat*" or "supraorbital stimulation" or "supraorbital neurostimulat*" or "t-SNS" or "SNS")
2. TI ("pain" or "pain management" or "chronic pain" or "intractable pain" or "migraine") or AB ("pain" or "pain management" or "chronic pain" or "intractable pain" or "migraine")
3. 1 and 2

Appendix L: Search Strategy for Intrathecal Pumps in Cancer and Non-Cancer Patients

Intrathecal Pumps inception-current, RCTs, Cancer and Non-cancer

MEDLINE; EMBASE

1. exp infusion pumps, implantable/
2. (intrathecal pump or neuromodulation or intrathecal drug administration or implantable infusion pump).tw,kw
3. Exp pain/ or exp pain management/ or exp cancer pain/ or exp chronic pain or exp pain clinics/ or exp shoulder pain/ or exp pelvic pain/ or exp pain, referred or exp pain, postoperative/ or exp pain measurement/ or exp neck pain/ or exp musculoskeletal pain/ or exp chest pain/ or exp breakthrough pain/
4. (pain or pain management or cancer pain or non-cancer pain or chronic pain or intractable pain).tw,kw
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. clinical trials as topic.sh.
13. randomly.ab.
14. trial.ti.
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp animals/ not humans.sh.
17. 16 not 17
18. 8 and 18

CINAHL

1. TI (“infusion pump*” or “intrathecal pump*” or “implantable infusion pump*” or “intrathecal”) or AB (“infusion pump*” or “intrathecal pump*” or “implantable infusion pump*” or “intrathecal”)

2. TI (“pain” or “pain management” or “chronic pain” or “cancer pain” or “pain clinic” or “shoulder pain” or “pelvic pain” or “referred pain” or “postoperative pain” or “pain measurement” or “neck pain” or “musculoskeletal pain” or “chest pain” or “breakthrough pain” or “intractable pain”) or AB (“pain” or “pain management” or “chronic pain” or “cancer pain” or “pain clinic” or “shoulder pain” or “pelvic pain” or “referred pain” or “postoperative pain” or “pain measurement” or “neck pain” or “musculoskeletal pain” or “chest pain” or “breakthrough pain” or “intractable pain”)

3. 1 and 2

Limited to randomized controlled trial

Appendix M: Intrathecal Pump Cancer and Non-Cancer Included Study Characteristics

Table 1. Intrathecal Pump Cancer and Non-cancer Pain Included Study Characteristics

Author, trial (if applicable), country, year	Technology and procedure	Intervention	Patient Characteristics	Primary outcome	Any secondary outcome(s)	Quality assessment
Deer, US, 2005	Medtronic Synchro-Medical intrathecal drug delivery devices; devices previously implanted	Control: intrathecal saline as a bridged bolus (0.5 mL/day for 1 week) Intervention: weekly escalating doses of 5, 10, 15, and 20 µg/hour of octreotide	Inclusion criteria: 18-70, previously implanted systems, did not have adequate pain relief with morphine or hydromorphone, known catheter length Type of pain: chronic, non-cancer n=18 Mean age (SD): not reported % male: not reported	Nausea <ul style="list-style-type: none"> Control: n=3 Intervention: n=0 Headache <ul style="list-style-type: none"> Control: n=1 Intervention: n=0 No changes in confusion, drowsiness, memory or visual deficits, weakness, numbness, or gait disturbance.	None reported	Some concerns
Deer, US, 2006	Medtronic Synchro-Medical intrathecal drug delivery devices; devices previously implanted	Control: intrathecal saline Intervention: weekly escalating doses of 5, 10, 15, and 20 µg/hour of octreotide	Inclusion criteria: previously implanted device; 18-70 years; unable to obtain adequate analgesia from both systemic and intrathecal therapy; known catheter length	Visual analog scale score <ul style="list-style-type: none"> Placebo: 7.6 5 µg/hr: 7.8 10 µg/hr: 7.6 15 µg/hr: 7.4 20 µg/hr: 7.2 Mean difference	None reported	Low risk of bias

			<p>Type of pain: chronic, intractable, non-cancer</p> <p>n=18</p> <p>Mean age (SD): 51.6 (13.0)</p> <p>% male: not reported</p>	<p>(placebo-octreotide at 20 µg/hour) in brief pain inventory (BPI)</p> <ul style="list-style-type: none"> • BPI worst pain: 0.50, p=.94 • BPI least pain: 0.30, p=1.00 • BPI average pain: 1.00, p=.28 • BPI pain now: 2.40, p=.25 • BPI percentage relief: -14.0, p=.63 		
Rauck, US, 2013	<p>SynchroMed® intrathecal pumps; pumps implanted into a subcutaneous pocket in the abdominal wall; catheter inserted percutaneously via lumbar puncture with the catheter tip placed into the intrathecal space at or below the T-10 vertebral level</p>	<p>Control: placebo (0.9% sodium chloride injection)</p> <p>Intervention: gabapentin injection (1, 6, or 30 mg/day)</p>	<p>Inclusion criteria: 18-70 years; not achieving adequate pain control</p> <p>Type of pain: chronic, intractable pain below the neck</p> <p>n=171 (167 included in primary efficacy analysis)</p> <p>Mean age (SD): 49.6 (not reported)</p> <p>% male: 42.4%</p>	<p>Mean change in numerical pain rating scale score (SD)</p> <ul style="list-style-type: none"> • Control: -0.48 (1.52) • 1 mg/day: -0.40 (1.33), p=.802 • 6 mg/day: -0.10 (0.99), p=.874 • 30 mg/day: 0.02 (1.11), p=.899 	<p>Mean change in brief pain inventory (SD)</p> <ul style="list-style-type: none"> • Control: -0.19 (1.59) • 1 mg/day: -0.45 (1.98) • 6 mg/day: 0.13 (1.52) • 30 mg/day: -0.37 (1.71), p=.375 <p>Mean change in quality of life, physical (SD)</p> <ul style="list-style-type: none"> • Control: 1.5 	Low risk of bias

					<p>(6.2)</p> <ul style="list-style-type: none"> • 1 mg/day: 1.2 (5.0) • 6 mg/day: -0.4 (5.6) • 30 mg/day: 1.2 (6.6), p=.257 <p>Mean change in quality of life, mental (SD)</p> <ul style="list-style-type: none"> • Control: 0.2 (8.5) • 1 mg/day: 3.7 (10.8) • 6 mg/day: -0.2 (10.5) • 30 mg/day: 2.7 (11.5), p=.392 <p>Mean change in beck depression inventory (SD)</p> <ul style="list-style-type: none"> • Control: -0.4 (8.5) • 1 mg/day: -3.0 (8.0) • 6 mg/day: -0.6 (9.4) • 30 mg/day: -1.1 (7.0), p=.565 <p>Change in mean</p>	
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					<p>daily opioid use (mg/day) (SD)</p> <ul style="list-style-type: none"> • Control: -3.0 (21.7) • 1 mg/day: -21.7 (97.8) • 6 mg/day: 4.1 (26.6) • 30 mg/day: 8.1 (51.4), p=.139 	
Smith & Coyne, The Cancer Pain Trial, US, 2005	Implantable drug delivery systems	<p>Control: comprehensive medical management only; received all pain therapy except spinally administered drugs, cordotomy, or other similar neurosurgical interventions</p> <p>Intervention: CMM + intrathecal pumps; received intrathecal morphine, or a different analgesia if morphine did not work</p>	<p>Inclusion criteria: documented cancer; visual analogue scale (VAS) pain scores consistently 5 or more of 10 despite pain management by their oncologist; taking at least 200 mg of oral morphine; had at least 3 months to live</p> <p>Type of pain: cancer associated pain</p> <p>n=99</p> <p>Mean age (SD): 58.6 (13.9) in control, 56.0 (13.4) in intervention</p> <p>% male: 62.3% in control, 53.3% in intervention</p>	<p>VAS score (SD)</p> <ul style="list-style-type: none"> • Before implant: 6.2 (2.8) • After implant: 4.5 (2.7), p=.011 <p>Composite drug toxicity score (SD)</p> <ul style="list-style-type: none"> • Before implant: 7.6 (4.8) • After implant: 3.8 (4.2), p<.0001 	None reported	High risk of bias
Smith, US, 2005	Implantable Drug	Comprehensive	Inclusion criteria:	>20% relief of	Average pain	Some

	Delivery Systems	medical management (CMM; control) vs. CMM + intrathecal pain therapy	<p>documented cancer; VAS pain scores >5/10 despite pain management; were on at least 200 mg of oral morphine or the equivalent; had at least 3 months to live</p> <p>Type of pain: intractable cancer-associated pain</p> <p>n=200</p> <p>Mean age (SD): 57.8 (13.7) in control, 56.2 (13.2) in intervention</p> <p>% male: 59.6% in control, 51.5% in intervention</p>	<p>pain and toxicity</p> <p>By 4 weeks</p> <ul style="list-style-type: none"> Control: 36.3% (33/91) Intervention: 67.3% (35/52), p=.002 <p>By 12 weeks</p> <ul style="list-style-type: none"> Control: 33.3% (15/45) Intervention: 57.9% (33/57), p=0.23 	<p>relief (% change)</p> <p>By 4 weeks</p> <ul style="list-style-type: none"> Control: 6.43 to 5.44 (20%) Intervention: 7.41 to 2.7 (55%), p=.0003 <p>By 12 weeks</p> <ul style="list-style-type: none"> Control: 6.73 to 4.13 (37%) Intervention: 6.68 to 2.30 (66%), p=.01 	concerns
Smith, for the Implantable Drug Delivery Systems Study Group, US, 2002	Implantable Drug Delivery Systems	Patients randomized into either comprehensive medical management (CMM, control) or intrathecal pain therapy	<p>Inclusion criteria: advanced cancer; VAS score higher than 5; taking 200 mg/d of oral morphine or the equivalent; pain expected to continue throughout life; age greater than 18 years; an expected life span of 3 months; were suitable for the IDDS</p> <p>Type of pain:</p>	<p>Changes in VAS score, mean (SD)</p> <ul style="list-style-type: none"> Control: 3.05 (3.16) Intervention: 3.90 (3.42), p=.055 <p>Changes in common toxicity criteria</p> <ul style="list-style-type: none"> Control: 1.09 (5.57) Intervention: 	<p>VAS pain reduced by 20%</p> <ul style="list-style-type: none"> Control: 51/72, 70.8%, Intervention: 60/71, 84.5%, p=.05 <p>Both pain and toxicity reduced</p> <ul style="list-style-type: none"> Control: 27/72, 37.5% Intervention: 	Some concerns

			refractory cancer-associated pain n=200 Mean age (SD): 57.8 (13.7) in control, 56.2 (13.2) in intervention % male: 59.6% in control, 51.5% in intervention	3.63 (5.43), p=.004	41/71, 57.7%, p=.02 Neither pain nor toxicity reduced • Control: 17/72, 23.6% • Intervention: 8/71, 11.3%, p=.05	
Staats, US, 2004	Intrathecal drug delivery system, either previously implanted or implanted for the trial	Patients received ziconotide or placebo for 5 days; starting @ 0.4 µg/h with incremental increases every 12 hours to a discretionary max doze of 2.4 µg/h [starting dose was decreased to 0.1 µg/h after the 1 st 48 participants]	Inclusion criteria: cancer or AIDS; VASPI score of 50 mm or higher Type of pain: cancer- or AIDS-associated pain n=108 Mean age (SD): 56.6 (2.07) in control, 55.3 (1.72) in intervention % male: 50% in both	% change in VASPI score • Control: 18.1% (95% CI: 17.3-49.4%) • Intervention: 53.1% (95% CI: 44.0-62.2%), p<.001	Patients with any serious adverse event • Control: 10.0% • Intervention: 30.6%	Low
Wallace, Elan Pharmaceuticals Inc., US, 2006	Intrathecal (IT) drug delivery system, either previously implanted or implanted for the trial; or an external IT catheter and infusion pump.	Patients received ziconotide or placebo for 5 days; 0.4 µg/h with incremental increases every 12 hours. This was decreased to 0.1	Inclusion criteria: 18 years or older; severe chronic, nonmalignant pain; VASPI score >50 mm; demonstrating unsatisfactory response to systemic	% change in VASPI score • Control: 6.0% (95% CI: 0.0-11.9%) • Intervention: 31.2% (95% CI: 24.6-	Patients responding to treatment • Control: 12.8% • Intervention: 33.7%, p<.001	Low

		<p>µg/h, to a maximum of 2.4 µg/h.</p>	<p>opioid therapy plus 2 other treatment options</p> <p>Type of pain: chronic, nonmalignant pain</p> <p>n=257</p> <p>Mean age (SD): 52.8 (12.43) in control, 51.6 (14.07) in intervention</p> <p>% male: 57.0% in control, 55.6% in intervention</p>	<p>37.9%), p<.001</p>	<p>Change in McGill Pain Questionnaire global score (SE)</p> <ul style="list-style-type: none"> • Control: 9.2 (3.3) • Intervention: 23.0 (3.8), p=.028 <p>Any adverse events</p> <ul style="list-style-type: none"> • Control: 72.1% • Intervention: 94.7%, p=.001 	
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Appendix N: Intrathecal Pump Risk of Bias Assessment

Table 1. Intrathecal Pump Included Study Risk of Bias Assessment

Study	Bias arising from randomization	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Final bias assessment
Deer	Low	Low	Low	Low	Some concerns	Some concerns
Deer	Low	Low	Low	Low	Low	Low
Rauck	Low	Low	Low	Low	Low	Low
Smith	Low	Low	Low	High	Low	High
Smith	Low	Some concerns	Low	Some concerns	Low	Some concerns
Smith	Low	Low	Low	Some concerns	Low	Some concerns
Staats	Low	Low	Low	Low	Low	Low
Wallace	Low	Low	Low	Low	Low	Low

Appendix O: Search Strategy for Patient Perspective

Patient Perspective Search Strategies

MEDLINE; EMBASE; all EMB reviews; PsychInfo

1. exp electric stimulation therapy/ or exp electric stimulation/ or exp deep brain stimulation/ or exp spinal cord stimulation/ or exp infusion pumps, implantable/
2. (spinal cord stimulation transcutaneous supraorbital nerve stimulation or peripheral nerve stimulation or peripheral nerve field stimulation or intrathecal pump or neuromodulation or electrical stimulation or neuromstimulation, or intrathecal drug administration or implantable infusion pump).tw,kw
3. Exp pain/ or exp pain management/ or exp cancer pain/ or exp chronic pain or exp pain clinics/ or exp shoulder pain/ or exp pelvic pain/ or exp pain, referred or exp pain, postoperative/ or exp pain measurement/ or exp neck pain/ or exp musculoskeletal pain/ or exp chest pain/ or exp breakthrough pain/
4. (pain or pain management or cancer pain or non-cancer pain or chronic pain or intractable pain).tw,kw
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp Patient Satisfaction/
9. Perception/
10. exp Qualitative Research/
11. exp Interview/
12. exp Focus Groups/
13. exp Choice Behavior/
14. exp Attitude to Health/ or Attitude/ or attitude to death/
15. (attitude* or experiences or opinions or perception* or perspective* or preference* or satisfaction* or views).tw.
16. (focus group* or interview* or qualitative or questionnaire* or survey or surveys or surveyed or grounded theory or phenomenolog*).tw.
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 7 and 17
19. limit 18 to animals
20. limit 18 to (animals and humans)

21. 19 not 20

22. 18 not 21

23. limit 22 to English language

Appendix P: SCS and FBSS Model

[Please contact HTA.Office@gov.bc.ca for more information]

Appendix Q: Intrathecal Pump Model

[Please contact HTA.Office@gov.bc.ca for more information]