SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stimulator, Spinal-Cord, Totally Implanted For Pain Relief

Device Trade Name: Restore, Itrel, Synergy, Intellis, and Vanta Spinal Cord Stimulation Systems; Pisces, Specify and Vectris Spinal Cord Stimulation Leads

Device Product Codes: LGW, QRB

Applicant's Name and Address: Medtronic Neuromodulation
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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P840001/S469

Date of FDA Notice of Approval: January 24, 2022

Medtronic's implantable neurostimulation system was first approved for spinal cord stimulation as an aid in the management of chronic, intractable pain for the trunk or limbs on Nov. 30, 1984 (PMA P840001). Since then, Medtronic has twice used published clinical literature to clarify or expand the Indications for Use (IFU) of the spinal cord stimulation systems. Supplements S045 and S047 requested approval to list specific pain etiologies along with the existing general indication. The IFU approved through those submissions are provided in Table 1 below; the etiologies added by each supplement are in italics. The current supplement was submitted to expand the IFU for Medtronic Spinal Cord Stimulator (SCS) Systems to include painful diabetic peripheral neuropathy (PDPN) of the lower extremities.

Table 1: SCS indication history

Submission	Approved Indications for Use
P840001 Approved 11/30/1984	The Medtronic ITREL Spinal Cord Stimulation System is indicated as an aid in the management of chronic, intractable pain of the trunk or limbs.
P840001/S045 Approved 6/22/2000	The Medtronic Implantable Neuromodulation System is indicated as an aid in the management of chronic intractable pain of the trunk and limbs, including chronic and intractable unilateral or bilateral pain associated with the following: • *Failed Back Syndrome or Low Back Syndrome or Failed Back* • *Radicular Pain Syndrome or Radiculopathies resulting in pain secondary to Failed Back Syndrome* • *Post-Laminectomy Pain* • *Multiple Back Operations* • *Unsuccessful Disk Surgery* • *Degenerative Disk Disease (DDD)/ Herniated Disk pain refractory to conservative and surgical interventions.*
P840001/S047 Approved 6/22/2000	The Medtronic Implantable Neuromodulation System is indicated as an aid in the management of chronic intractable pain of the trunk or limbs, including unilateral or bilateral pain associated with the following: • Failed Back Syndrome or Low Back Syndrome or Failed Back • Radicular Pain Syndrome or Radiculopathies resulting in pain secondary to Failed Back Syndrome or Herniated Disc • Post-Laminectomy Pain • Multiple Back Operations • Unsuccessful Disk Surgery • Degenerative Disk Disease (DDD)/ Herniated Disk pain refractory to conservative and surgical interventions. • *Peripheral Causalgia* • *Epidural Fibrosis* • *Arachnoiditis or Lumbar Adhesive Arachnoiditis* • *Complex Regional Pain Syndrome (CRPS) or Reflex Sympathetic Dystrophy (RSD) or Causalgia*

*New indications in *italicized text* above were approved in the corresponding submissions.

II. INDICATIONS FOR USE

This device is indicated for spinal cord stimulation (SCS) systems as an aid in the management of chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain associated with the following conditions:

- Failed Back Syndrome (FBS) or low back syndrome or failed back
- Radicular pain syndrome or radiculopathies resulting in pain secondary to FBS or herniated disk
- Postlaminectomy pain
- Multiple back operations
- Unsuccessful disk surgery
- Degenerative Disk Disease (DDD)/herniated disk pain refractory to conservative and surgical interventions
- Peripheral causalgia
- Epidural fibrosis
- Arachnoiditis or lumbar adhesive arachnoiditis
- Complex Regional Pain Syndrome (CRPS), Reflex Sympathetic Dystrophy (RSD), or causalgia
- Diabetic peripheral neuropathy of the lower extremities

III. CONTRAINDICATIONS

Diathermy - Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Medtronic implantable neurostimulation system labeling. Safety information was updated in accordance with the most recent American Diabetes Association's Standard of Medical Care in Diabetes to address the increased risk and potential complications for diabetic peripheral neuropathy patients. Additional warnings were added to provide guidance for managing patients presenting with risk factors or sub-optimal glycemic control.

V. DEVICE DESCRIPTION

System Description

The Medtronic SCS system uses an implantable multi-programmable

neurostimulation system to deliver electrical stimulation to neural targets in the spinal cord. A Medtronic SCS system is comprised of the following components:

The major components of an SCS system include:

- Leads and Extensions – Leads are used for both the stimulation trial, or evaluation, and implanted SCS therapy. The lead delivers the stimulation to the targeted nerve through electrodes on the end of the lead. The extension connect the lead to the neurostimulator.
- External Neurostimulator (ENS) – The ENS provides stimulation for patients during an evaluation or during intraoperative testing.
- Implantable Neurostimulator (INS) – The INS provides stimulation for the patient after a successful evaluation.
- Clinician Programmer – Used by the clinician to configure and maintain the patient's therapy through adjustment of the available therapy parameters (amplitude, rate, pulse width, cycling, soft start and stop and electrode configuration) and the creation of programs which consist of a specific set of values for each of the therapy parameters.
- Patient Programmer – Used by the patient to maintain their therapy through stimulation intensity adjustment and program selection. The programs are pre-set by the clinician.
- Patient recharger – Used by the patient to charge the battery of a rechargeable INS. A plug-in charger recharges the patient recharger.

The SCS product portfolio includes several implantable neurostimulators and leads to best serve individual patient and clinician needs, such as primary cell and rechargeable neurostimulators and variable electrode size and spacing in the leads.

Stimulation pulses are controlled in terms of output amplitude (milliamps; mA), pulse width (μsec) and rate (Hz). Multiple electrodes on a lead may be activated. Some programming restrictions apply, based on options selected. Electrical current generated by the neurostimulator travels along the leads to the distal electrodes.

Figure 1 shows a representation of a SCS system powered by a neurostimulator.

Principles of Operation

Spinal cord stimulation is the application of mild electrical stimulation to the spinal cord to relieve chronic, intractable pain of the trunk and/or limbs. Neurostimulation therapy is based on the gate control theory of pain. The stimulation of specific nerve targets is thought to interfere with the perception of pain transmitted or generated by abnormally functioning neural structures. The function of the stimulation system is accomplished with a power source and one or more leads, with the optional use of lead extensions. For Medtronic SCS systems,

an implantable neurostimulator (INS) is the power source that generates and controls the electrical stimulation, which is delivered to electrodes at the distal end of the lead(s) in the spine, as shown in Figure 1.

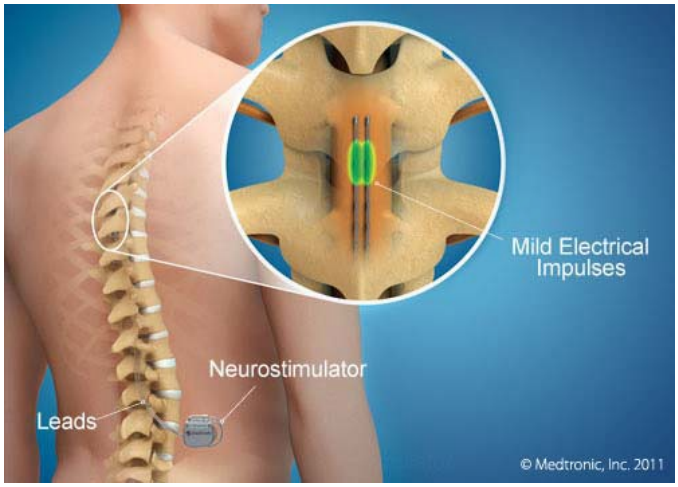

Figure 1. Representation of implanted SCS system.

System Components

All of the Medtronic SCS System components within the scope of this submission are commercially available in the United States and have been approved by the FDA through supplements to PMA P840001. Table 2 lists all implantable system components and the associated document control numbers. There are no changes proposed for these devices; the only changes proposed are to the labeling concerning the Indications for Use.

Table 2: Implantable SCS system components and control devices

Device model number and product family name	Doc control number
Neurostimulators	
97715 Intellis™ Implantable Neurostimulator System with AdaptiveStim™ Technology	P840001/S344
97716 Intellis™ Implantable Neurostimulator System	P840001/S344
97725 Wireless External Neurostimulator	P840001/S344
977005 Sequentia™ LT Implantable Neurostimulator	P840001/S471

977006 Vanta™ with AdaptiveStim™ Implantable Neurostimulator	P840001/S471
Leads	
977A160 Vectris® SureScan® MRI 1x8 SC (Subcompact) Lead Kit	P840001/S219
977A175 Vectris® SureScan® MRI 1x8 SC (Subcompact) Lead Kit	P840001/S219
977A190 Vectris® SureScan® MRI 1x8 SC (Subcompact) Lead Kit	P840001/S219
977A260 Vectris® SureScan® MRI 1x8 Compact Lead Kit	P840001/S219
977A275 Vectris® SureScan® MRI 1x8 Compact Lead Kit	P840001/S219
977A290 Vectris® SureScan® MRI 1x8 Compact Lead Kit	P840001/S219
977C165 Specify® SureScan® MRI 5-6-5 Lead	P840001/S308
977C190 Specify® SureScan® MRI 5-6-5 Lead	P840001/S308
977C265 Specify® SureScan® MRI 2x8 Lead	P840001/S308
977C290 Specify® SureScan® MRI 2x8 Lead	P840001/S308
977D160 Vectris® 1x8 SC (Subcompact) Trial Screening Lead Kit	P840001/S219
977D260 Vectris® 1x8 Compact Trial Screening Lead Kit	P840001/S219
Extension	
37081 1x8 Extension	P840001/S074
Patient Control Devices	
97745 Controller	P840001/S344
97755 Recharger	P840001/S344
Clinician Control Devices	
A710 Intellis Clinical Programmer Application	P840001/S344
8880T2 Communicator	P840001/S344

A71200 Vanta™ / Sequentia™ LT Clinician Programmer Application (CPA)	P840001/S471
A71300 Stimulation Trialing Clinician Programmer Application (CTA)	P840001/S471
A72200 MyStim PC Patient Programming Application (PPA)	P840001/S471

In addition, accessory kits are used in conjunction with Medtronic SCS implantable systems and are commercially available in the US.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of chronic, intractable pain associated with PDPN of the lower extremities. Treatment of PDPN is based on two different approaches: glycemic control and symptomatic pain treatment. Treatment of the underlying diabetes, if possible, is generally the primary approach to pain management. Improvements in control of blood-sugar levels for diabetic neuropathy patients is initially addressed. Pharmacologic treatments are delivered to address the symptoms of pain. These include tricyclic anti-depressants, anti-convulsants (α-2-δ modulators: gabapentin, pregabalin or valproate), and selective serotonin/norepinephrine re-uptake inhibitors (SSRI/SNRI). It is recommended that comorbidities should be evaluated before selecting a first-line therapy. Subsequently, if a patient is refractory to one of the first-line therapies, a second or combination of other first-line drugs should be prescribed. Second- line therapies include opioid analgesics for acute rescue therapy. The emergent recognition of dependence syndromes associated with the use of opioids complicates the treatment of symptoms refractory to first-line treatments. Non-pharmacologic treatments include physical therapy, cognitive therapy, and transcutaneous nerve stimulation (TENS). These therapies would be provided in conjunction or following first-line medical treatment, but before more invasive therapies are considered, and only under the direction of a pain management specialist. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Medtronic implantable neurostimulation system for the treatment of chronic intractable pain of the trunk and/or limbs is approved for commercial distribution in Argentina, Australia, Belarus, Bosnia and Herzegovina, Brazil, Canada, China. Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, European Union, Guatemala, Indonesia, Israel, Japan, Kazakhstan, Korea, South, Kuwait, Malaysia, Mexico, Morocco, Peru, Saudi Arabia, Singapore, South Africa, Taiwan, Thailand, Turkey, Ukraine, USA, Uruguay, and Vietnam. The device has not been

withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of a Medtronic implantable neurostimulation system.

The implantation of a spinal cord stimulation system involves risks that are similar to other spinal procedures. In addition to those risks associated with surgery, the following adverse events may occur with implantation or use of a neurostimulation system:

- Allergic or immune system response to the implanted materials
- Infection
- Lead, extension, or neurostimulator erosion through the skin or migration
- Leakage of cerebrospinal fluid
- Loss of pain relief may return patients to their underlying pain condition
- Patients on anticoagulation therapies may be at greater risk for postoperative complications such as hematomas that can result in paralysis
- Persistent pain at the neurostimulator site
- Placement of the epidural lead-extension is a surgical procedure that may expose patients to risks of epidural hemorrhage, hematoma, or paralysis
- Radicular chest wall stimulation
- Seroma or hematoma at the neurostimulator site
- Change in stimulation, possibly related to cellular changes around the electrode(s), shifts in electrode position, loose electrical connections, lead or extension fractures, which has been described by some patients as uncomfortable stimulation (jolting or shocking sensation).
- Formation of reactive tissue around the lead in the epidural space can result in delayed spinal cord compression and paralysis, requiring surgical intervention. Time to onset can range from weeks to many years after implant.
- Stimulation-dependent gastrointestinal symptoms such as nausea, diarrhea, incontinence, or constipation
- Stimulation-dependent bladder symptoms such as urinary retention, incontinence, or frequency

IX. SUMMARY OF NONCLINICAL STUDIES

Pre-clinical studies previously submitted to FDA in the Original PMA application (P840001) and supplements continue to support the safety of the commercially available Medtronic implantable neurostimulation system for treatment of chronic

intractable pain of the trunk and/or limbs. No additional preclinical studies were required to evaluate the safety of Medtronic SCS therapy for the treatment of PDPN of the lower extremities. The previously approved supplements which support the Medtronic SCS therapy system and its components are listed above in Table 2.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

A Medtronic implantable neurostimulation system is indicated for spinal cord stimulation systems as an aid in the management of chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain. The safety and effectiveness of a Medtronic implantable neurostimulation system has been previously established for indicated patients suffering from a variety of conditions (see Section I, Table 1).

The clinical evidence to support safety and effective use of the Medtronic implantable neurostimulation system in the diabetic neuropathy population is based on a systematic review of published clinical scientific literature of commercially available SCS systems. Primary evidence comes from two randomized controlled trials in patients with painful diabetic peripheral neuropathy (PDPN). Additional supplemental clinical evidence for safety was identified through a literature review, and the Medtronic product surveillance registry data, investigating adverse event data related to SCS use in patients with painful diabetic neuropathy (PDN), and included reports reflecting the experience of patients treated with SCS for any condition where a diagnosis of diabetes was considered. PDN encompasses many different types of neuropathy, including PDPN, autonomic neuropathy, proximal neuropathy, and mononeuropathy.

A. Study Design

The safety and effectiveness of the Medtronic implantable neurostimulation system to treat PDN was based on clinical safety outcome data from the Medtronic Product Surveillance Registry (PSR) and a systematic review of published scientific literature reporting on the use of any commercially available spinal cord stimulation (SCS) systems for the treatment of chronic intractable pain in a diabetic population. A systematic review of published literature was conducted by searching Embase and MEDLINE for terms relating to SCS and diabetes. Additionally, a systematic search of the published literature was conducted to identify recent guidelines on perioperative care of diabetic patients.

Safety

Safety objective: Identify risks relevant to SCS to which diabetic patients are

predisposed and to characterize the safety profile of SCS to treat PDN.

The safety profile of Medtronic implantable neurostimulation systems to treat PDN was characterized through analysis of data from Medtronic's Product Surveillance Registry (PSR) and published scientific literature. The analysis characterized the overall safety profile by common adverse events, as well as specifically examining the risks to which the diabetic population are pre-disposed such as inherent surgical complications that may occur more frequently or have greater impact in these patients. Publications reflecting the experience of patients treated with SCS for PDN and patients treated with SCS for any condition where a diagnosis of diabetes was considered were included. Publications reporting on studies where adverse events were reported in a comprehensive manner were pooled with data from the PSR to create an overall safety profile.

Effectiveness

Effectiveness objective: Characterize the clinical benefits related to pain relief for SCS used to treat PDN, when compared to the standard-of-care.

The effectiveness of Medtronic implantable neurostimulation systems to treat PDN was demonstrated through analysis of clinical study results identified from the systematic review of published scientific literature. The probability of treatment success (aka Responder Rate or Proportion of successfully treated subjects) defined by a specific threshold for pain reduction or Patient Global Impression of Change (PGIC) rating and the magnitude of pain relief as measured through reduction in pain scores from a Numeric Rating Scale (NRS) or Visual Analog Scale (VAS) were considered in determining effectiveness.

Additionally, all publications reporting on the non-comparative studies (i.e. prospective single-arm studies) were included and summarized.

B. Medtronic Product Surveillance Registry (PSR)

The PSR is sponsored by Medtronic and is comprised of a global network of hospitals, clinics, and clinicians from which reliable "real-world" product safety and patient clinical outcome information is generated. The purpose of the registry is to provide continuing evaluation and periodic reporting of safety and effectiveness of market-released products for their intended use. The registry was revised in 2010 to collect more details on the pain sub-indication, including diabetic neuropathy as a primary or 'other' indication. Any indication that was not collected as the primary indication is referred to as a secondary indication.

Data selection

Patients were identified as receiving SCS for the treatment of diabetic neuropathy if they met one of the following criteria:

1. Primary indication was specified as diabetic neuropathy ("Primary"), or
2. Primary indication was "Other chronic pain" and the free text specified diabetic neuropathy ("Primary (Other)"), or
3. Secondary indication was specified as diabetic neuropathy or the free text for an "other" secondary indication specified diabetic neuropathy ("Secondary").

Diabetic neuropathy patients with active follow-up time in the PSR after the 2010 revision were included.

C. Literature Search Strategy

The databases searched include Embase and MEDLINE. Elsevier provides access on a single search platform via Embase.com. The databases were searched to ensure comprehensive coverage of globally published clinical evidence for medical device products and therapies. Embase, published by Elsevier, provides access to biomedical literature, with over 32 million records from over 8,300 currently published journals from 95 countries. MEDLINE is the largest component of PubMed (http://pubmed.gov/), the online database of biomedical journal citations and abstracts created by the U.S. National Library of Medicine (NLM®). MEDLINE contains bibliographic citations and author abstracts from more than 5,600 medical and life science journals published in the United States and 70 other countries. The database contains over 21 million citations.

Two separate systematic searches and reviews were conducted. For both searches, the publications identified from databases were assessed for inclusion in the review though 2 steps. First, two reviewers independently screened initial search results for the selection criteria. Next, full-text copies of the selected publications were assessed independently by the same two reviewers for inclusion as final selections. Differences in selection between the 2 reviewers were discussed to confirm selection or rejection. A third party was not necessary to resolve disputed selections.

1. Clinical practice guidelines on perioperative care of diabetic patients
    a. Search terms (including expanded terms): Diabetes AND Clinical practice guideline or consensus statement AND peri-, post-, pre- operative or surgical
    b. Search dates: 2016-2021
    c. Selection criteria: The guideline must provide specific recommendations for steps to be taken to avoid complications

of surgery in a diabetic population. The publication must include a comprehensive list of specific steps, which are generalizable to SCS procedures.

2. Safety and effectiveness of SCS to treat PDN
    a. Search terms (including expanded terms): Diabetes AND spinal cord stimulation or dorsal column stimulation
    b. Search dates: 1984-2021
    c. Selection criteria:
        i. Safety: Publication must include data on a distinctly identifiable diabetic population and report comprehensive detail on adverse events or an analysis of the impact of a diabetic state on a safety-related outcome
        ii. effectiveness: Publication must include data from prospective studies on SCS to treat PDN with quantifiable information regarding pain reduction, probability of treatment success, or quality of life improvements. Any available meta-analyses were included if the report synthesized new data based on prospective studies.

Results of search and screening

Clinical practice guidelines for perioperative care of diabetic patients

Initial screening was performed on 178 titles and abstracts resulting in the selection of 39 publications for full-text review. After full-text review, 11 publications were selected for inclusion. Guidelines are summarized in Table 3.

Table 3. Selected Guidelines

Author and Title	Summary	Recommendations	Noted complications
Berhe et al. Intl. J. Surg. 2017[1] Guideline on peri-operative glycemic control for adult patient with diabetic mellitus: Resource limited areas	Review and guideline of diabetic patients undergoing surgery, differentiated by minor or major surgery, aimed at resource limited health systems	• Urinalysis and electrolyte test results should be available at pre-operative screening • Prioritize operation for first of the day • Fast before surgery, unless procedure later in day, then light meal with half dose of fast acting insulin • When fasting, check glucose every 2 hours, and 1 hour prior to surgery • Target range for blood glucose: o 108-180 mg/dL and 72-216 mg/dL is acceptable o Postpone elective surgery if over 300 mg/dL or HbA1c >69 mmol/L, and consult specialist for management	• Post-operative infection • Surgery stress causing diabetic ketoacidosis • Hyperglycemia • Hyperosmolar state • Increased morbidity and mortality • Hypoglycemia leading to somnolence, confusion, seizures, irreversible neurological injuries • Impaired wound healing • Increased occurrence in cardiac arrythmias

Chan et al. Anaesth. Intensive Care Med. 2020[2] Preoperative cardiac optimization	Guideline for peri-operative cardiac optimization, considering diabetes among other comorbidities	• Peri-operative target for blood glucose of 6-10 mmol/L • Glycemic control should be checked at time of surgery. • Diabetic patient should be identified early in pre-operative pathway • Tests for comorbidities should be conducted including electroconvulsive therapy (ECT), urea and electrolytes for all patients • Surgery should be scheduled early in the day to avoid disruption of glycemic control	Autonomic neuropathy can cause perioperative hemodynamic instability

Author and Title	Summary	Recommendations	Noted complications
Cheisson et al. Anaesthesia, critical care & pain medicine. 2018[3] Perioperative management of adult diabetic patients. Intraoperative period.	Practice guideline focusing on the intra-operative management of diabetic patients from the French Society of Anaesthesia and Intensive Care and the French Society for the Study of Diabetes	• Avoid prolonged fasting by scheduling procedures early in the day • Have a blood glucose goal of 5-10 mmol/L, avoiding hypoglycemia • If insulin is required, use fast acting analog subcutaneously with electronic syringe with IV glucose • Replace insulin pump with immediate IV management during procedure • Monitor glucose every 1-2 hours and potassium every 4 hours if under insulin control, and consider 3.8 mmol/L hypoglycemia requiring intervention • All solutes may be used, including Ringer's lactate, in the peri-operative period • Peri-operative control is dictated by 3 factors: diabetes type, pre-operative control, and type of surgery • Manage risk of nausea and vomiting as to facilitate resumption of food intake after surgery • Manage post-operative pain	• Infections • Delayed wound healing • Increased morbidity and mortality

		closely to avoid hyperglycemia	
Cheisson et al. Anaesthesia, critical care & pain medicine. 2018[4] Perioperative management of adult diabetic patients. Postoperative period.	Practice guideline focusing on the post-operative management of diabetic patients from the French Society of Anaesthesia and Intensive Care and the French Society for the Study of Diabetes	• Maintain subcutaneous insulin via electronic syringe until glucose stabilizes (<10 mmol/L) and discontinue when normal feeding resumes • Manage discontinuation with appropriate slow and fast acting insulins Resume treatments based on diabetes type, management regimen, and post-operative glucose levels	Hyperglycemia (ketoacidosis) and hypoglycemia

Author and Title	Summary	Recommendations	Noted complications
Dortch et al. Aesthetic surgery journal. 2016[5] Perioperative Glycemic Control in Plastic Surgery: Review and Discussion of an Institutional Protocol	Practice guideline for care of diabetic patients undergoing plastic surgery with specific procedure examples as well as a generalized protocol from the Mayo Clinic	• Outpatient guidelines: Pre-operative screening to include HbA1c • If HbA1c > 8%, refer to primary care physician for optimization • Monitor blood glucose in postanaesthesia unit • Goal of < 180 mg/dL following surgery Patients should be instructed to resume customary monitoring and resume fast acting insulin if discontinued prior to surgery	• Wound infection • Wound healing • Impaired immunologic defense mechanisms • Increased mortality
Livshetz & Nett. Tech. Orthop. 2019[6] Perioperative Management of Diabetes for Total Joint Arthoplasty: A Consensus Article	Review covering questions of screening, HbA1c level cut-offs, and guidelines for practice in total joint arthroplasty	• Given lack of consensus for HbA1c limits of 7%, <8% seems prudent to mitigate risks • All patients should be screened for HbA1c levels and orthopedic surgery should be postponed if spot glucose checks results in >200 mg/dL on the day of surgery • ADA guidelines should be followed for peri-operative glucose control (pre-prandial 80-130 mg/dL and < 180 mg/dL post-prandial)	• Wound complications • Thrombosis • Surgical site infection

Author and Title	Summary	Recommendations	Noted complications
Mumdzic & Munir, Surgery. 2020[7] Perioperative management of diabetes and corticosteroid supplementation	Peri-operative guidance on peri-operative diabetes management and supplemental corticosteroid treatment	• Pre-operative evaluation should include history, kidney function, blood count and coagulation profile, updated HbA1c • Refer for expert optimization of glucose control if HbA1c > 8.5% for elective surgeries • Intra-operative levels of 6-10 mmol/L should be the goal (6-12 mmol/L is acceptable) • Diet-managed Type 2 diabetics may not require therapy and are not at risk for hypoglycemia, though if they become hyperglycemic they can be managed with fast acting insulin • Management of glucose should be made with consideration of surgery complexity as to how many missed meals will be experienced	• Increased postoperative morbidity and mortality

Author and Title	Summary	Recommendations	Noted complications
Robinson et al. Anaesth. Intensive Care Med. 2020[8] Perioperative management of diabetes	Review of perioperative diabetes management with background information, management steps and recommendations on special populations/situations	• Referrals for surgery should include HbA1c in last 3 months, BMI, eGFR, and accurate medication list • Thorough pre-operative assessment for cardiovascular disease, diabetic nephropathy, autonomic neuropathy, peripheral neuropathy, diabetic retinopathy, obesity, autoimmune disease, and HIV • Postpone elective surgery if HbA1c > 69 mmol/L to confirm optimization and consult with multidisciplinary team to proceed • Minimize fasting time by early scheduling (first of day or within first 1/3rd of schedule) Perioperative glucose management plan should be made based on pre-operative levels to adjust medications including insulin • Intra-operative levels of 6-10 mmol/L should be the goal (6-12 mmol/L is acceptable) • Patients should be provided with information on managing their diabetes upon discharge	• Post-operative infection (surgical site or systemic) • Cardiovascular events • Acute kidney injury • Stroke

Author and Title	Summary	Recommendations	Noted complications
Simha & Shah. JAMA. 2019[9] Perioperative Glucose Control in Patients With Diabetes Undergoing Elective Surgery.	Description of management of blood glucose in perioperative period with guidance on insulin management	• HbA1c should be check in all patients • Postpone elective surgery if HbA1c > 8% and would require intensifying of diabetes management strategies • Postpone elective surgery in severe hyperglycemia (>250 mg/dL) • Reduce insulin prior to surgery (50-75%), with half-dose on day of surgery if glucose is elevated • Schedule procedure in the AM to reduce duration of fasting • Intra-operative management to <180 mg/dL without causing hypoglycemia • Re-check blood glucose post-operatively, with a goal of pre-prandial 100-140 mg/dL and random 100-180 mg/dL	• Wound infection • Pneumonia • Sepsis • Cardiovascular events
Stryker. The Journal of arthroplasty. 2016[10] Modifying Risk Factors: Strategies That Work Diabetes Mellitus.	Peri-operative guidance on checking and managing blood glucose in patients, with and without diabetes diagnosis undergoing total joint arthroplasty	• Peri-operative screening in all patients, with >200 mg/dL further screened for HbA1c • Goal of <7% HbA1c, though may be higher with individual cases	• Delayed wound healing • Deep infection • Thrombosis • Mortality

Author and Title	Summary	Recommendations	Noted complications
		• Unmanageable levels should be referred to dietician or patient's primary physician • Short acting insulin or oral regimens withheld on morning of surgery, with long acting agents or infusion pumps continued • Post-operative insulin regimens can resume after resumption of regular diet	
Wang et al. Clinical neurology and neurosurgery. 2021[11] Preoperative optimization for patients undergoing elective spine surgery.	General perioperative guideline on management of patients in regard to medications, diabetes, hypertension, smoking, renal function, BMI, psychosocial aspects, and frailty.	• HbA1c goal of < 7% • Pre-prandial glucose 90-130 mg/dL • Post-prandial glucose < 180 mg/dL • First-start surgical case (early in the surgery day) • Insulin Glucose Tolerance Test (GTT), IV management perioperative) for >200 mg/dL • Continue home insulin, discontinue atypical hyperglycemic agents • Cancellation of procedure if in diabetic ketoacidosis or >400 mg/dL	• Delayed wound healing • Infection • Thrombosis • Mortality

Safety and effectiveness

Initial screening was performed on 319 titles and abstracts resulting in the selection of 69 publications for full-text review. After full text review, articles were selected for inclusion based on safety, effectiveness, or as meta-analyses. The following number of publications were selected for each category:

- Safety: 19 publications. Several studies resulted in multiple publications. Safety information was extracted from the publication with the longest follow-up from each study that included comprehensive adverse event information and is included in Table 4.
- Effectiveness: 12 publications. Several studies resulted in multiple publications. Effectiveness data was extracted from all publications and included in total for each cohort.
- Meta-analyses: 2 publications reported meta-analyses of randomized controlled studies of SCS to treat PDN. The reports are summarized in Table 6.

Table 4: Selected reports of SCS to treat a diabetic patient population

Cohort (Authors and Years)	Summary of Study Design	Relevant Safety Data	Relevance and Limitations
Tesfaye (1996)[12] **and Daousi (2005)**[13]	Prospective observational study of SCS to treat PDN with a double-blind test stimulation period and pain ratings of background and peak pain with the stimulator on or off 10 subjects, 8 receiving implant followed for clinical performance outcomes Follow-up: 3 and 6 months and end of study with a median of 14 moths and a range=9-20 months. (Tesfaye, 1996) Patients were then followed-up at 3 and 7 years after the study end. (Daousi, 2005)	Of 8 subjects receiving SCS implant: 3 deaths at 2 mo, 2 yr, and 4 yr. All from myocardial infarction 1 explant due to lack of pain relief 2 superficial infections treated with antibiotics 2 lead migration with revision 2 skin peeling at antenna site 1 hematoma at implant site w/out clinical impact 1 lead failure due to trauma, replaced	Relevance: The earliest report of a prospective study specifically examining the use of SCS to treat PDN. Relatively long follow-up allowed for characterization of the comorbid health burden which leads to early mortality in this population. Limitations: Small, Non-comparative study. SCS technology is from a previous generation of single-lead systems and externally powered neurostimulators, limiting the potential flexibility for reprogramming and patient compliance.

Cohort (Authors and Years)	Summary of Study Design	Relevant Safety Data	Relevance and Limitations
Petrakis (1999)[14]	Study of SCS delivered to diabetic patients with peripheral arterial occlusive disease examining changes in microcirculation and predictors of success 64 subjects Mean follow-up duration of 58 months (range 20-128 months)	8 battery replacement procedures following normal end of device life 2 lead migrations requiring lead revision 2 Infections requiring explant	Relevance: Use of Medtronic SCS systems. Includes a description of the use of SCS in a specific diabetic population. Peripheral Vascular Diseases are common in diabetic patients and represent and overlap in affected populations. Limitation: Non-comparative study. SCS technology is from a previous generation of single-lead systems limiting the potential flexibility for reprogramming and patient compliance.

TenVaarwerk (1999)[15]	Multi-center retrospective cohort study of patients treated with SCS for refractory Angina Pectoris over a 10-year period to determine morbidity and mortality characteristics 517 patients, 14% identified as having Insulin Dependent Diabetes Mellitus (IDDM) Median follow-up of 23 months	Percentage of patients with IDDM in cohort was 14%. IDDM patients were relatively over-represented in the population who died and under-represented in the population who survived. -Died = 20% -Survived = 13% -p = 0.05 Multi-variate analysis significantly correlated IDDM with mortality	Relevance: Report of SCS in a population where a co-factor of diabetes could be described related to safety. Limitations: Within study comparison was not a prospective group allocation factor. The population was not PDN patients and of a group where 100% presented with an intractable cardiovascular disease condition.

Cohort (Authors and Years)	Summary of Study Design	Relevant Safety Data	Relevance and Limitations
de Vos (2009)[16]	Prospective observational study of pain relief and microcirculatory function in PDN patients treated with SCS 11 subjects 6-month primary endpoint and 30-month follow-up	2 lead/extension failures with revisions 1 mild infection treated with antibiotics 1 death described to be unrelated to SCS	Relevance: Use of Medtronic SCS system. Prospective pilot study that led to a larger multicenter RCT Limitations: Small, single-center study without comparator group. Use of single 4-contact lead system.
Mekhail (2011)[17]	Single-center retrospective case series to review indications and complications of SCS to treat Failed Back Surgery Syndrome (FBSS), Complex Regional Pain Syndrome (CRPS), Peripheral Vascular Disease (PVD), visceral pain, neuropathy over a 5-year period 707 patients (8% with diabetes diagnosis) Mean follow-up of 3 years and 5 months, range from 3 months to 7 years	Overall infection rate: 4% Infection rate of diabetic population: 9% p = 0.188 chi-square	Relevance: Large case series that allowed for analysis of the co-factor of diabetes as a predictor of infection, concluding no statistical association. Long-term follow-up included Limitations: Potential inclusion bias in retrospective design. Smaller diabetic population may have reduced ability to detect difference in infection rate.

Cohort (Authors and Years)	Summary of Study Design	Relevant Safety Data	Relevance and Limitations
Pluijms (2012[18]; 2015[19]), Slangen (2013[20]; 2014[21]), van Beek (2015[22]; 2018[23])	Multi-center cohort of subjects included in a prospective single-study and a RCT of SCS to treat PDN with analyses of predictors of success. Patients were pooled from all implanted subjects reported in Pluijms, 2012 and Slangen, 2014 48 subjects 5-year follow-up	13 subjects with implantable neurostimulator (INS) replacement due to battery depletion, 5 of those subjects had 2 replacements (18 total) 10 subjects reporting pocket pain with 1 leading to revision due to persistent pain, without complete resolution of pain 9 subjects reporting uncomfortable stimulation 6 subjects were explanted due to loss of therapeutic effect. 5 lead migrations with revision 4 lead failures with replacement 2 infections leading to explant 1 dural puncture and CSF leak during trial procedure leading to subdural hematoma and subsequent death	Relevance: Use of Medtronic SCS systems. Long-term follow-up of a cohort of patients included in a single arm study as well as those treated as part of a multi-center RCT of subjects with PDN treated with SCS, including control arm subjects who crossed over to the treatment arm. Long-term follow-up of 5 years. Limitations: Lack of individual patient data to determine the number of adverse events in each patient, other than for battery replacement at the expected end-of-service of devices

Cohort (Authors and Years)	Summary of Study Design	Relevant Safety Data	Relevance and Limitations
de Vos (2014)[24]	RCT, Parallel design with 2:1 allocation comparing SCS + conventional medical practice vs conventional medical practice to treat of PDN 60 Subjects (40:20) 6 months primary endpoint on pain measures	Procedure related adverse events: 2 pain at INS 2 required additional lead placed to cover painful area 1 each of lead migration, infection during trail period, coagulopathy resulting in prolonged hospitalization Non-study related (potentially due to underlying condition): SCS group: 2 infections causing unstable glucose 1 femur fracture 1 cardiac arrest Control group: 2 infections 1 each of Carotid artery stenosis, Myocardial infarction, atrial fibrillation episode, coronary bypass surgery	Relevance: Provides detailed safety information, including relatedness, from subjects with PDN treated with SCS. Limitations: SCS system used from another manufacturer, though with equivalent characteristics. Limited follow-up of 6 months. Lack of individual patient data to determine the number of adverse events in each patient

Cohort (Authors and Years)	Summary of Study Design	Relevant Safety Data	Relevance and Limitations
Bir (2016)[25]	Retrospective review of SCS patients treated for FBSS or chronic back pain examining the predictors of revision of the SCS system 141 patients Follow-up: Median 31.5 months (range=3-166)	Revision Free Survival curves plotted for non-diabetic vs diabetic patients and there was no significant difference detected (p=0.98)	Relevance: Large review that allowed for analysis of the co-factor of diabetes as a predictor of all cause system survival concluding no significant impact of the co-factor. Limitations: Potential inclusion bias in retrospective design, Not specific to PDN
Hoelzer (2017)[26]	Multi-center cohort study reviewing infection rates and risk factors associated with SCS over a 7-year period in patients treated for FBSS, CRPS, Post-Herpetic Neuralgia, and other chronic pain conditions 1,960 permanent implants 777 surgical revisions 2,737 total patients (461 patients with diabetes) 12-month follow up window	Surgical Site Infection (SSI) rate of 2.45% SSI rates for diabetic state: -Yes: 1.99% -No: 2.54% -p = 0.49	Relevance: Large review that allowed for analysis of the co-factor of diabetes as a predictor of surgical site infection, concluding no significant difference. Limitations: Potential inclusion bias in retrospective design, Not specific to PDN

Cohort (Authors and Years)	Summary of Study Design	Relevant Safety Data	Relevance and Limitations
Falowski (2019)[27]	Retrospective analysis of the payer databases over a 5-year period to characterize infection risk factors in chronic pain patients treated with SCS based on demographics, comorbidities, and clinical characteristics 5,563 with initial INS 1,052 replacement INS 6,615 patents in total (1,663 patients with diabetes) 12-month follow-up window	Overall infection rate of 3.11% Proportions of population of initial implants with/without infection: -Type 1 Diabetes Mellitus (DM) = 4.07%/3.32% (p = 0.5904) -Type 2 DM = 24.02%/22.02% (p = 0.4551) Logistic Regression for Infection Within 12 Months: -Type 1 DM -Odds ratio: 1.335 -p = 0.4391 -Type 2 DM -Odds Ratio: 1.124 -p = 0.6121	Relevance: Analysis of predictors of infection by multiple factors concluding that diabetes was not a predictor of surgical site infection. Payer database likely reliable source as few events would go unrecorded. Limitations: Payer database limited data to implanted subjects, excluding the opportunity for trial exposure.
Galan (2020)[28]	Sub-analysis of PDN patients from a prospective cohort of peripheral neuropathy patients treated with 10 kHz SCS 8 subjects 12 months follow-up	8 Non-serious adverse events in 3 subjects of which 2 were study-related: seroma and pain in extremity 3 serious adverse events in 3 subjects of which 1 was study related: wound dehiscence	Relevance: Cohort of PDN patients treated with an SCS system reporting detailed adverse event data. 12-months of follow-up Limitations: Data from other manufacturer where therapy delivery would be unlikely to provide information related to overstimulation events. Small cohort size.

Cohort (Authors and Years)	Summary of Study Design	Relevant Safety Data	Relevance and Limitations
Antonovich (2021)[29]	Retrospective review of chronic pain patients treated with SCS comparing reoperation rates associated with either percutaneous or paddle leads. 271 patients, 65 with a diagnosis of diabetes	65 patients indicated a diagnosis of diabetes (22.34%) A diagnosis of diabetes was not associated with reoperation (univariate Hazard Ratio = 0.70; p = 0.197).	Relevance: Large contemporary data set describing safety outcomes analyzing diabetes as a co-factor, concluding that it was not statistically associated with re-operation Limitations. Single center retrospective study could allow for inclusion bias
Petersen (2021)[30]	Multi-center, randomized (1:1) trial comparing the treatment of 10 kHz SCS to conventional management of PDN 216 subjects (103 control and 113 SCS with 104 exposed to at least trial stimulation) 6 months follow-up	18 adverse events in 14 subjects treated with SCS Study related AEs: 3 Infection 2 Wound dehiscence 2 Explants 1 each of impaired healing, device extrusion, incision site pain, IPG discomfort, lead migration, contact dermatitis, utricaria, radiculopathy, uncomfortable stimulation, gastroesophageal reflux, myalgia, arthralgia, hyporeflexia	Relevance: Safety data from large multi-center RCT in PDN patients comparing outcomes to the standard of care. Provided detailed adverse event information including related and unrelated events. Limitations: Data from other manufacturer where therapy delivery would be unlikely to provide information related to overstimulation events, though one is reported. Data from individual subjects unavailable to determine multiple events in individual subjects.

Table 5: Reports on effectiveness of SCS to treat PDN

Cohort (Authors and Years)	Summary of Study Design	Effectiveness Data	Relevance and Limitations
Tesfaye (1996)[12] **and Daousi (2005)**[13]	Prospective observational study of SCS to treat PDN with a double-blind test stimulation period and pain ratings of background and peak pain with the stimulator on or off 10 subjects, 8 receiving implant followed for clinical performance outcomes Follow-up: 3 and 6 months and end of study with a median of 14 moths and a range=9-20 months. (Tesfaye, 1996) Patients were then followed-up at 3 and 7 years after the study end. (Daousi, 2005)	Trial success: 80% (8/10) Percent of subjects with pain relief and continued SCS use (n=10): 6 mos: 60% 3.3 years: 60% 7.5 years: 40% (100% of surviving implanted patients) Magnitude of pain relief as % difference in median pain score between stimulation ON and OFF, at 6 months: 'Background pain': 58% 'Peak pain': 59% No change in sensory thresholds, nerve conduction, or HbA1c	Relevance: The earliest report of a prospective study specifically examining the use of SCS to treat PDN. Relatively long follow-up Limitations: Small size with limited number surviving for longest time-point. Non-comparative study. SCS technology is from a previous generation of single-lead systems and externally powered neurostimulators, limiting the potential flexibility for reprogramming and patient compliance.

Cohort (Authors and Years)	Summary of Study Design	Effectiveness Data	Relevance and Limitations
de Vos (2009)[16]	Prospective observational study of pain relief and microcirculatory function in PDN patients treated with SCS 11 subjects 6-month primary endpoint and 30-month follow-up	Trial success: 82% Subjects with ≥50% pain relief (n=11) 6 mo = 55% 12 mo = 64% 30 mo = 64% Subjects with ≥30% pain relief (n=11) 6 mo = 73% 12 mo = 73% 30 mo = 73% Average pain relief 6 mo = 55.8% (n=9) 12 mo = 70.1% (n=9) 30 mo = 70.1% n=9)	Relevance: Use of Medtronic SCS system. Prospective pilot study that lead to a larger multicenter RCT Limitations: Small, single-center study without comparator group. Use of single 4-contact lead system.

Cohort (Authors and Years)	Summary of Study Design	Effectiveness Data	Relevance and Limitations
de Vos (2014a)[31]	Single-arm study of chronic pain patients treated with SCS comparing traditional SCS to another programming approach. 48 subjects, 12 with PDN Mean duration of treatment for PDN group: 1.8 years	Average pain relief at follow-up: 60%	Relevance: Publication provided a subset of subjects with PDN and compared to a novel programming method. Data from baseline and standard SCS programming showed meaningful pain relief. Limitations: Single center study with small sample of subpopulation. Detail on baseline pain score collection was limited. Possible selection bias by selecting already implanted subjects.

Cohort (Authors and Years)	Summary of Study Design	Effectiveness Data	Relevance and Limitations
de Vos (2014b)[24] **and Duarte (2016)**[32]	RCT, Parallel design with 2:1 allocation comparing SCS + conventional medical practice vs conventional medical practice to treat of PDN 60 Subjects (40:20) 6 months primary endpoint on pain measures (de Vos, 2014) and Quality of Life (Duarte, 2016)	Trial success: 93% Primary endpoint of proportion of subjects reporting ≥ 50% pain relief at 6 months: SCS: 63% Control: 5% $p < 0.001$ Average pain relief at 6 months -SCS 57.5% -Control: 0% EuroQoL EQ-5D (0-1 scale) SCS: 0.39 improvement Control: 0.00 improvement EQ-5D VAS (0-100) SCS: 12-point improvement Control: 7-point improvement	Relevance: RCT of standard SCS programming to treat PDN compared to conventional treatment. SCS programming consistent with standard SCS. Demonstrated robust effectiveness and significant average pain relief. Significant improvements in EQ-5D measures related to Quality of Life Limitations: SCS system used from another manufacturer, though with equivalent characteristics. Limited follow-up of 6 months. Lack of individual patient data to perform additional analysis. No blinding which could result in biased outcome measures.

Cohort (Authors and Years)	Summary of Study Design	Effectiveness Data	Relevance and Limitations
Pluijms (2012[18]; 2015[19]) and Slangen (2013)[20]	Prospective, single center, single-arm study of SCS to treat PDN. Pain relief was the primary measure. (Pluijms, 2012). Heat-evoked potentials and manual sensory testing were measured (Pluijms 2015) 15 subjects (11 implanted with SCS system) 3, 6, and 12-month follow-up (Pluijms 2012) and through 36 months (Slangen, 2013)	Trial success: 73% Subjects with treatment success as measured by ≥50% pain relief in day or nighttime pain or PGIC rating of 'much improved or 'very much improved' (n=15): at 12 months: 67% Daytime pain relief at 12 months: 51.7% Implanted subjects with treatment success as measured by ≥50% pain relief in day or nighttime pain or Patient Global Impression of Change (PGIC) rating of 'much improved or 'very much improved' (n=11): 12 months: 91% 24 months: 55% 36 months: 68% Subjects with improved EQ-5D 12 mo: 64% 24 mo: 55% 36 mo: 64% No differences were found between responders and non-responders in heat-evoked potentials or sensory testing	Relevance: Use of Medtronic SCS systems. Pilot study to support later RCT. Showed meaningful pain relief and sustained effects to 36 months. Limitations: Small, single-center study. Lack of individual patient data to perform further analysis.

Cohort (Authors and Years)	Summary of Study Design	Effectiveness Data	Relevance and Limitations
Slangen (2014)[21] **and Van Beek (2015)**[22]	Multi-center, randomized (3:2) trial comparing SCS + Best Medical Treatment (BMT) vs BMT to treat PDN 36 subjects (22:14) 6-month primary endpoint (Slangen, 2014) 24-month follow up (Van Beek, 2015)	SCS trial success rate: 77% Primary endpoint of subjects with treatment success as measured by ≥50% pain relief in day or nighttime pain or PGIC rating of 'much improved or 'very much improved': SCS: 59% Control: 7% p = 0.009 Pain reduction at 6 months: SCS: 44% Control: 0% EQ-5D utility score change at 6 months: SCS: 0.25 improvement Control: 0.00 improvement Implanted subjects with treatment success as measured by ≥50% pain relief in day or nighttime pain or PGIC rating of 'much improved or 'very much improved': 3 mo: 94% 6 mo: 76% 9 mo: 76% 12 mo: 71% 24 mo: 65%	Relevance: Use of Medtronic SCS systems. RCT of subjects with PDN treated with SCS, including control arm subjects who crossed over to the treatment arm. Long-term follow-up of 2 years. Demonstrated robust effectiveness and meaningful pain relief. Limitations: Though appropriately powered based on pilot study, was small in size. Lack of individual patient data to perform additional analyses. No blinding which could result in biased outcome measures. Improvement seen with SCS treatment did not reach levels of significance.

Cohort (Authors and Years)	Summary of Study Design	Effectiveness Data	Relevance and Limitations
Van Beek (2018)[23] -Combined cohort from Pluijms 2012 and Slangen 2014	Multi-center cohort study of SCS to treat PDN with analyses of predictors of success. Patients were pooled from all implanted subjects reported in Pluijms 2012 and Slangen 2014 48 subjects 5-year follow-up	Subjects with treatment success as measured by ≥50% pain relief in day or nighttime pain or PGIC rating of 'much improved or 'very much improved': 12 mo: 86% 24 mo: 71% 36 mo: 77% 48 mo: 67% 50 mo: 55% Pain score reduction (NRS) for daytime (d) or nighttime (n) pain: 12 mo: (d) 43%; (n) 42% 24 mo: (d) 39%; (n) 39% 36 mo: (d) 43%; (n) 42% 48 mo: (d) 37%; (n) 34% 60 mo: (d) 36%; (n) 31% Kaplan-Meier survival analysis showed 80% of implanted subjects still used the SCS system after 5 years. Higher Michigan Diabetic Neuropathy Score (MDNS) was associated with failure and higher baseline nighttime pain was associated with success.	Relevance: Use of Medtronic SCS systems. Long-term follow-up of a cohort of patients included in a single arm study as well as those treated as part of a multi-center RCT of subjects with PDN treated with SCS, including control arm subjects who crossed over to the treatment arm. Long-term follow-up of 5 years. Demonstrated a high degree of treatment success in implanted subjects through long term follow-up. Provided analysis on predictor of success based on baseline severity of PDN Limitations: Lack of individual patient data to perform additional analyses. No control group after control arm crossed over to SCS treatment. Loss to follow-up over 5 years represents some missing data that could bias conclusions.

Table 6. Selected Meta-analyses on SCS to treat PDN

Author/Title	Methods Summary	Results
Raghu et al. (2020)[33] Invasive Electrical Neuromodulation for the Treatment of Painful Diabetic Neuropathy: Systematic Review and Meta-Analysis	MEDLINE and Embase were searched through 10 January 2020. Two reviewers independently screened publications and extracted data. Quantitative meta-analysis was performed with pain scores converted to a standard 100-point scale. Randomized controlled trial (RCT) scores were pooled using the inverse variance method and expressed as mean differences. The Cochrane risk of bias tool was used to assess bias. PROSPERO registration: CRD42019135591	Mean difference in pain score reduction (0-100 scale) of 37.84 (95% CI 28.83 to 46.85; I^2 = 0%). Pooled mean difference for EQ-5D = 0.16 (CI 0.02 to 0.30; I^2=0%) and EQ-VAS = 11.21 (CI 2.26 to 20.16) Risk of bias: *"Both RCTs had a low risk of bias in multiple categories However, allocation concealment and blinding to outcome were unclear, and the nature of SCS necessitates a high risk of performance bias."*
Duarte et al. (2021)[34] Spinal cord stimulation for the management of painful diabetic neuropathy: a systematic review and meta-analysis of individual patient and aggregate data	MEDLINE, CENTRAL, and Embase were searched from inception until 21MAY2020. Two reviewers independently screened titles and abstracts and full-text publications were again reviewed independently. Cochrane risk of bias tool (RoB 2.0) was used to assess bias. The primary outcome was pain intensity at the last follow-up time point available. PROSPERO registration: CRD42020204390	Mean difference in pain score reduction (0-10 scale) of 3.13 (95% CI 4.19 to 2.08; I^2 = 0%) Risk of bias: *"Both RCTs were judged to have a low risk of bias for the domains of the process of randomisation, deviations from intended interventions, and level of missing outcome data. However, both RCTs were judged to have a high risk of bias for outcome measurement as these were open label trials."*

D. Safety and Effectiveness Results

1. Safety Results

Clinical practice guidelines on the perioperative care of diabetic patients

Recommendations on the perioperative care of diabetic patients were extracted from the individual publications. Recommended precautions frequently included preoperative screening for patients with a history of comorbidities or poor glycemic control. The level of glycemic control, as reflected by HbA1c (%, or mmol/mol), varied and it was commonly described as having no strong consensus. Several guidelines set a threshold of an HbA1c level of 8% as a point to consider delaying surgery, if it was necessary to ensure that the patient has optimized their glycemic control. The most common recommendations were for surgical timing in the morning to minimize fasting time and management of insulin and medications in the perioperative period. Many recommendations are applicable to care provided by anesthesiologists during intra-operative management of hyperglycemic or hypoglycemic states. The guidelines cited specific complications to which diabetic patients are known to be predisposed. Delayed wound healing, infection, cardiovascular events (including myocardial infarction, stroke, and deep vein thrombosis), and general morbidity or mortality were most commonly referenced.

From the guidelines, citations describing the incremental risks were reverse traced to primary sources. The sources described rates of events in the diabetic population as well as the relative risk levels (described in Odds or Hazard Ratios). Sources were screened for similarity of populations studied as compared to SCS (elective, orthopedic or spinal surgery, etc.). Most noted perioperative events were more likely to occur in diabetic patients, with Odds Ratios ranging from 1.52 to 6.07. Several reports described the increased odds of infection. Overall, diabetic patients are approximately twice as likely to experience infection. Delayed wound healing likely contributes to this increased risk by being over 6 times more likely in a patient with an HbA1c greater than 8%.[35] Myocardial infarction was identified in univariate analysis as potentially being more likely but did not reach significance in multivariate analyses. The likelihood of stroke was elevated in the same cohort (OR = 3.42; 95% CI = 1.87 to 6.25; $p < 0.001$).[35]

Slangen et al. (2014) reported one subject death following a dural puncture and subsequent CSF leak leading to a cranial subdural hematoma.[21] Ha et al. (2016) reported data from craniotomy procedures concluding that diabetic patients may be at higher risk of CSF leak (Univariate regression model; $p = 0.021$).[36] Though a Multivariate regression model did not find significant relation between diabetes and CSF leak (Odds Ratio = 1.82; $p = 0.448$).[36] The more invasive nature of craniotomy relative to SCS lead placement somewhat limits the translation of this

concern to SCS procedures. The report in the literature on SCS to treat PDN and the univariate association warrants consideration. Wang et al. (2014) reported increased incidence of subdural hematoma in diabetic patients (log-rank test, $p < 0.0001$).[37] Cox proportional hazard modeling resulted in an adjusted Hazard Ratio = 1.63. The analysis considered all causes including traumatic and non-traumatic events initiating the subdural hematoma. The authors hypothesized that the prevalence of cardiovascular disease and subsequent use of anti-coagulants as well as renal disease may contribute to increase in bleeding tendency or that brain atrophy and subsequent stretching of bridging veins increases the likelihood of vessel tearing as explanations for this increase in relative risk.

Selected references are included in Table 7. The table also includes the risk of fluctuation in blood glucose in response to an adverse event as described by de Vos et al. (2014).[24]

Table 7. Perioperative complications and relative risk in diabetic patients

Generalized Events	**Observed Rate in Diabetic Population (source, intervention, rate)**	**Relative Risk for Diabetic Population**
Delayed wound healing	Han et al. (2013)[38], Total Knee Arthroplasty, Wound complication rate = **6.6%**	Han et al. (2013): OR HbA1c > 8 = 6.07
Infection: surgical site, systemic, pneumonia	Golden et al. (1999)[39], Coronary artery surgery, Infection rate: **24.3%** (SSI Leg = 10.9%, SSI sternum = 5.6%)	Golden et al. (1999): progressive trend with blood glucose and OR for infection. OR mean blood glucose (MBG) 207-229 mg/dL=1.17; 230-252 mg/dL =1.86; 253-353 mg/dL=1.72
	Brown et al. (2007)[40], Lumbar fusion surgery, Infection rate **0.68%**	Brown et al. (2007): OR = 1.52
	Anderson et al. (2017)[41], Spine surgery, Infection rate for highest risk groups undergoing laminectomy = **2.3%**	Anderson et al. (2017): OR = 2.04
	Marchant et al. (2009)[35], Total Joint Arthroplasty, Infection rate: **0.38%** in controlled diabetes and **1.18%** in uncontrolled diabetes	Marchant et al. (2009): OR = 2.28
Cardiovascular events: stroke, deep vein thrombosis (DVT), myocardial infarction (MI),	Marchant et al. (2009)[35], Total Joint Arthroplasty,	Marchant et al. (2009): Myocardial infarction OR =

Hemodynamic instability	Myocardial infarction = 0.01% Stroke = 0.2%	1.54 in uncontrolled diabetics (p>0.05); Stroke OR = 3.42
CSF leak-subdural hematoma	Wang et al. (2014)[37], All cause, Rate of subdural hematoma in diabetic population = 2.04/1000 person years	Wang et al. (2014) Adjusted hazard ratio of 1.63 for diabetic patients for subdural hematoma
	Ha et al. (2016)[36], Craniotomy, Rates not specific to diabetic patients	Ha et al. (2016): OR = 1.82 for CSF leak in diabetic patients
Fluctuation of glucose	de Vos et al. (2014)[24], SCS to treat PDN, rate of glucose fluctuation in diabetic patients subsequent to an infection = **5%**	N/A - Experienced only by diabetics

Data on diabetic and specifically PDN patients treated with SCS is included in the following sections. The safety profile of SCS use in diabetic populations appears to be similar as what is observed in non-diabetic patients in most reports, with some exceptions. The similarity in safety profile does not eliminate the fact that diabetic patients are at increased risks for perioperative complications based on broader data collection on similar elective procedures. To address the incremental risks and avoid complications in diabetic patients, safety information in device labeling has been supplemented to include additional warnings and adverse event listings. Additional information includes warnings of the potential for increased frequency or severity of events as well as selecting and managing patients presenting with risk factors or sub-optimal glycemic control. The included recommendations are in line with the most recent American Diabetes Association standards of care on diabetic patients in the hospital setting.[42]

Registry data on PDN patients treated with SCS

Available data on 67 patients treated with SCS between April 15, 2010 and October 31, 2020 for PDN as a primary or secondary indication are included in the safety analysis. The 67 patients in the PDN analysis set had a median of 15 months of device exposure post-2010, ranging from 0 to 110 months. A total of 51 events related to the device, therapy, or procedure occurred in 22 patients. Adverse events (ex. device site pain, infection, wound healing issues) and device events (lead migration, neurostimulator battery failure, lead fracture) are distinguished, with some events classified as both adverse and device events. Thirty-nine adverse events occurred in 18 patients (27%). Twenty-six device events occurred in 14 patients (21%). Both an adverse event and device event was recorded for 14 of the events.

A survival analysis (freedom from event) was conducted by comparing outcomes for the PDN patient population to a non-PDN population enrolled in the Registry (n = 2733). Infection, device site pain, wound problems, cerebrospinal fluid (CSF) leak, lead migration, and lead fracture events were compared. Only infection was shown as having a statistical difference between PDN and non-PDN patients ($p = 0.02$), with PDN patients having a higher risk of infection (hazard ratio (HR) of 2.8).

Data on common adverse events in SCS recorded as part of the Registry are included in Table 8 along with data from published literature.

Published literature – Safety

Common Adverse events

Studies which included detailed adverse event information were pooled to assess common adverse event occurrences. Table 8 presents study data grouped by

reports of common patient cohorts and by populations defined specifically by PDN or by those reporting on patients with diabetes in general (DM).

Table 8. Common Adverse Events

		n[a]=	Adverse Event counts (%)						
			Infection	Lead migration	Lead failure	Device site swelling or pain	Hematoma/ erosion/ wound	CSF leak	Uncomfortable stimulation/ stimulation issue
PDN	PSR	67	5 (7.5)	11 (16.4)	4 (6.0)	5 (7.5)	1 (1.5)	1 (1.5)	5 (7.5)
	Tesfaye (1996)-Daousi (2005)[13,12]	10	2 (20)	2 (20)	1 (10)	-	1 (10)	-	-
	de Vos (2009)[16]	11	1 (9.1)		2 (18.2)	-	-	-	-
	de Vos (2014)[24]	40	3 (7.5)[c]	1 (2.5)		2 (5)	-	-	2 (5)
	Pluijms (2012)[18]-Slangen (2013)[20] -Slangen (2014)[21]-van Beek (2015)[22]-van Beek (2018)[23b]	49	2 (4.1)	5 (10.2)	4 (8.2)	10 (20.4)	-	1 (2)	9 (18.4)
	Galan (2020)[28]	9	-	-	-	1 (11)	-	-	-
	Petersen (2021)[30]	104	3 (2.9)	1 (1.0)	-	2 (1.9)	4 (3.8)	-	1 (1.0)
DM	Petrakis (1999)[14]	64	2 (3.1)	2 (3.1)	-	-	-	-	-
	Mekhail (2011)[17]	56	5 (8.9)	-	-	-	-	-	-
	Hoelzer (2017)[26]	461	9 (2.0)	-	-	-	-	-	-
	Falowoski (2019)[27]	1663	59 (3.5)	-	-	-	-	-	-
	Range		2.0%-20%	1%-20%	6.0%-18.2%	1.9%-20.4%	1.5%-10%	1.5%-2.0%	1.0%-18.4%

[a] Sample size reflects patients or subjects exposed to SCS (at least an SCS trial) as described in the individual reports

SCS in diabetic populations

Published literature describing SCS to treat PDN and published clinical practice guidelines on peri-operative care of diabetic patients provide information on specific inherent risks which may be of concern for diabetic patients when it comes to the delivery and management of SCS therapy.

- **Infection**

Data on PDN patients treated with SCS demonstrated a 5.5% (range: 2.9% to 20%) infection rate. In the overall population of diabetic patients included in published literature and the PSR, the infection rate was 3.6%. Data from 3 large retrospective cohorts concluded that either diabetes was not a predictor of infection or there was no statistical difference observed in the infection rate between diabetic and non-diabetic patients.[27,26,17] An analysis comparing the infection rate between PDN and non-PDN patients participating in the PSR revealed a significant difference ($p = 0.02$; HR of 2.8). A recent systematic review of SCS complications across all indications reported an infection rate of 4.9% (range: 2.5%-10%).[43]

- **Wound healing**

Data on diabetic patients treated with SCS demonstrated 1.7% (range: 1.5% to 10%) rate of issues with wound healing. Delayed wound healing may contribute to infection and the rates may be underestimated due to subsequent appreciation of a more serious adverse event.

- **Cardiovascular events**

Several reports of subject or patient death attributed to myocardial infarction (4) or heart failure (1) were included in the available data on SCS to treat PDN.[13,24] None were reported to be related to SCS procedures or therapy, though patients with uncontrolled diabetes may have an elevated risk for cardiovascular events in the perioperative period. In an analysis of outcomes in patients undergoing elective orthopedic surgery, patients with poor glycemic control showed a non-significant trend towards greater odds of myocardial infarction and a significantly greater odds of stroke (Odds Ratio 3.42 CI: 1.87-6.25; $p < 0.001$).[35]

- **Dural puncture and CSF leak**

Slangen et al. (2014) reported one subject death following a dural puncture and subsequent CSF leak leading to a cranial subdural hematoma.[21] Ha et al. (2016) reported data from non-SCS procedures concluding that diabetic patients may be

at higher risk of CSF leak (Univariate regression model; p = 0.021). Though a Multivariate regression model did not find significant relation between diabetes and CSF leak (Odds Ratio = 1.82; p = 0.448).[36] Wang et al. (2014) reported increased incidence of subdural hematoma in diabetic patients (log-rank test, p < 0.0001). Cox proportional hazard modeling resulted in an adjusted Hazard Ratio = 1.63.[37]

- **Glycemic control**

de Vos et al. (2014) reported 2 subjects experiencing fluctuations in blood glucose levels following infections.[24] While these were assessed by authors as unrelated to SCS, the physiologic stress of surgery or any adverse event may impact glycemic control.

- **Mortality and morbidity: Patient deaths and other serious adverse events**

The cohort described in the PSR data above, there was one death. The event was described as cardiac heart failure and unrelated to SCS.

TenVaarwerk et al. published a report on the factors associated with morbidity and mortality in patients treated with SCS for refractory Angina Pectoris.[15] The multi- center retrospective studied 517 subjects implanted over a 10-year period, 14% of which were identified as having insulin dependent Diabetes Mellitus (IDDM). A multi-variate analysis significantly correlated IDDM with mortality. Overall, in this cohort, 66% of the patients had experienced myocardial infarction, 68% had three vessel disease, and in 24% the left ventricular ejection fraction (LVEF) was < 40%. The majority of patients had undergone interventional cardiac procedures such as angioplasty or bypass surgery. The benefits of SCS to treat angina may outweigh the risks for this population with intractable pain, though the health status of the population in this report limits the translation of this data to the PDN population.

In the 10-subject study reported on in Tesfaye et al. and Daousi et al. there were 3 deaths over the course of 7 year follow up.[13,12] The deaths occurred at 2 months, 2 years, and 4 years after implant. All were from myocardial infarction and all had reported effective pain relief up until the time of death.

In the 11-subject study published by de Vos et al. (2009), they reported one subject death due to causes unrelated to SCS.[16]

In the randomized controlled trial (RCT) reported by de Vos et al. (2014), one subject experienced prolonged hospitalization related to the implant procedure due to a coagulopathy.[24] The publication also described one subject in the SCS group

with a cardiac arrest (no other detail or comment of subject death) as unrelated to the study procedure.

SCS-specific events

Device events may be associated with or the cause of certain adverse events. Several reports describe hardware-specific complication rates.

- **SCS system survival**

Bir et al. (2016) reported on the rates of overall system survival for 141 patients treated at a single center and compared the diabetic population relative to the non- diabetic population. System survival was defined as being free from revision for any reason including device failure, migration, infection, or loss of effect. The revision- free survival time was 35 months for the diabetic population and 43 months for the non-diabetic population. The authors reported no statistical difference between the revision free survival time (log rank p = 0.98).[25]

Antonovich et al. (2021) conducted a retrospective review of patients treated with SCS for chronic pain and found diabetes was not associated with re-operation (p = 0.197).[29]

- **Lead migration and lead failure**

Lead migration was reported in 5 publications and the PSR. The rate of lead migration reported in these studies ranged from 1% to 20% with an average of 6.2% across all publications that reported events in detail and the PSR. A recent systematic review of SCS complications reported a lead migration rate ranging from 2.1 to 27%, with a mean rate of 15.5%.[43]

Lead failure was reported in 3 publications and the PSR. The rate of lead failure reported in these studies ranged from 6% to 18.2% with an average of 3.1% across all publications that reported events in detail and the PSR.

Lead migration and lead failure were compared in PDN and non-PDN populations within the PSR. No significant difference was found for device survival due to lead migration or lead failure between the two groups.

2. Effectiveness Results

Non-comparative studies

Seven publications include data on 4 prospective single-arm studies of SCS to treat PDN.[13,16,31,18–20,12] SCS trial success rates ranged from 73% to 82%. The proportion of subjects assessed as successfully treated ranged from 55% to 67% in the early phase of treatment (6-12 months) and from 40% to 68% at long-term follow-up (30 months to 7 years). Average pain relief ranged from 52% to 70%.

Comparative studies

Two randomized studies investigating the use of SCS to treat PDN were described across 4 publications.[24,32,21,22] Table 9 presents a comparison of clinical study results from the two publications reporting on the primary outcomes.

Table 9. Details of publications describing randomized studies on PDN

Publication	**Slangen et al.**[21]	**de Vos et al.**[24]
Sponsor	Maastricht University Medical Center (NCT01162993)	Medisch Spectrum Twente (ISRCTN03269533)
Population	Diabetes Meletus patients suffering from moderate to severe painful diabetic polyneuropathy in the lower limbs refractory to conventional treatments for more than 12 months Reporting an NPRS ≥ 5 Between 18 and 80 years of age	Patients suffering from diabetic neuropathic pain in the lower extremities for more than 1 year and refractory to conventional treatments Reporting a VAS pain rating ≥ 50 mm ≥ 18 years of age
Design-allocation	Open Label, Randomized, Parallel assignment (3:2)	Open Label, Randomized, Parallel assignment (2:1)
Comparator	Best medical treatment (BMT)	Best conventional medical practice (BCMP)
Sample size (countries)	36 from 2 centers (NL)	60 from 7 centers (NL, BE, DK, DE)
Primary endpoint	≥ 50% pain reduction during daytime or nighttime or a score of ≥ 6 on a 7- point Likert scale of the PGIC scale for pain and sleep	Treatment success at 6 months, ≥50% pain reduction
Publication Date	Nov 2014	Nov 2014

The demographic characteristics of subjects in both studies were similar for age, duration of disease (diabetes and PDN), and gender. Fewer Type I diabetic subjects were included in Slangen et al., though in both studies the majority of subjects were diagnosed as Type II diabetics. Subject demographics for each study are presented in Table 10.

Table 10. Comparison of study demographics

Demographic	Slangen et al.[21]	de Vos et al.[24]
Age (years)	56.9	59.0
Duration of diabetes mellitus (years)	12.7	16.3
Duration of Pain (years)	5.5	7.0
Male	67%	63%
Female	33%	37%
Type I	11%	25%
Type II	89%	75%

To illustrate the comparable outcomes associated with SCS or control group therapies of the population studied, the subject pain-related outcome measure averages are shown in Table 11. Pain-related outcomes were similar between studies with slightly greater reductions in pain reported by de Vos et al. Neither control group achieved sufficient reduction in average pain; however, one subject in the control arm reported treatment success.

Table 11. Comparison of pain measures (95% CI)

Pain rating[a]	Slangen et al.[21]		de Vos et al.[24]	
	SCS (n=22)	Control (n=14)	SCS (n=40)	Control (n=20)
Baseline	7.1 (6.3-7.9)	6.5 (5.5-7.5)	7.3 (6.8-7.8)	6.7 (5.9-7.5)
6-month	4[d] (2.6-5.4)	6.5 (5.4-7.6)	3.1 (2.2-4.0)	6.7 (5.7-7.7)
Pain relief[b]	44%	0%	58%	0%
Responder Rate[c]	59% (36%-79%)	7% (0%-34%)	63% (46%-77%)	5% (0%-25%)

[a] VAS (0-100 mm) and NRS (0-10) were normalized to a 0-10 scale

[b] Confidence interval for the percent mean change have not been calculated because biased due to the percent asymmetry

[c] Study design defined successful pain relief by different measures

[d] n=19 subjects with available data for pain scores at 6-months

Combined data from comparative studies

Both comparative studies were multi-center, open-label, randomized studies comparing SCS to treat a subject population with intractable painful diabetic neuropathy of the lower extremities to the standard-of-care (aka conventional management) with a primary endpoint at 6 months of follow-up. Data from both studies were pooled and are presented in Table 12. Average values were weighted by the number of subjects in the respective SCS and Control treatment groups for each study.

Table 12. Combined subject measures (95% CI)

Measure	*SCS (n=62)*	*Control (n=34)*
Age (years)	57.7	59.1
Duration of DM (years)	14.8	15.2
Duration of Pain (years)	6.6	6.1
Male	65%	65%
Female	35%	35%
Type I	21%	18%
Type II	79%	82%
Average Baseline pain rating	7.2 (6.5-10)	6.6 (5.7-9.6)
Average 6-month pain rating	3.4 (2.1-4.4)	6.6 (5.6-9.5)
Average Pain reduction[a]	53%	0%
Responder Rate per protocol[b,c]	61% (48%-73%)	6% (0%-20%)
Responder Rate ≥ 50% reduction in pain[c]	55% (42%-68%)	3% (0%-15%)
Responder Rate per protocol as-treated[d]	70% (56%-82%)	6% (0%-20%)
Responder rate ≥ 50% reduction in pain as-treated[d]	63% (49%-76%)	3% (0%-15%)

[a] Confidence interval for the percent mean change have not been calculated because biased due to the percent asymmetry

[b] Each study design defined successful pain relief by different measures

[c] Analysis of all randomized subjects in an intent-to-treat approach

[d] Including only subjects who received an SCS system implant

Meta-analysis for comparative studies

A meta-analysis of Responder Rate (≥50% pain relief) from the two RCTs was performed. An analysis of heterogeneity between the studies supported homogenization (Cochran's Q=0.658, p = 0.419; Higgin's I^2 test < 0). The confidence intervals of these studies overlap and the estimate of ORs are

consistent demonstrating subjects treated with SCS are more likely to achieve ≥50% pain relief at 6 months. The overall OR is 17.4 (95% CI 3.8-79.7) in favor of treatment success with SCS treatment for PDN ($p < 0.001$).

Long-term effectiveness

van Beek et al. (2015) published 24-month follow up on the remaining 17 implanted subjects randomized to the SCS group in the study reported by Slangen et al. (2014).[21,22] After 2 years, 65% of subjects were reported as treatment success. EQ-5D scores were significantly improved through 24-months. Seventy-nine percent of subjects had available data through the 24-month timepoint.

van Beek et al. (2018) published long-term follow-up results for subjects from the studies reported by Pluijms et al (2012) and Slangen et al. (2014).[18,21,23] Forty-eight subjects (40 with permanent implant) were included in the analysis for follow-up to 5 years. Treatment success was defined as ≥50% pain relief in day or nighttime pain or PGIC rating of 'much improved or 'very much improved'. Treatment success was observed in 86%, 71%,77%, 67%, and 55% at 1 (n = 36), 2 (n = 35), 3 (n = 34), 4 (n
= 30), and 5 (n = 22) years, respectively. A Michigan Diabetic Neuropathy Score (0 to 3 scale) of 3 at baseline was associated with treatment failure during the 5-year follow-up (HR 3.9; p = 0.014). This suggests patients with severe neuropathy may be less likely to experience treatment success.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was leveraged to support the reasonable assurance of safety and effectiveness of the subject device in the pediatric sub-population of adolescents aged 18-21.

In accordance with section 515A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), an analysis was conducted on the available information about pediatric subpopulations who suffer from chronic, intractable pain of the trunk and/or limbs. The pediatric population is defined as patients 21 years of age or younger. Medtronic's implantable neurostimulation system is approved for use in patients age 18 and older.

A search was conducted using MEDLINE and EMBASE on March 31, 2020 to identify the prevalence and incidence of Failed Back Syndrome, FBSS, Low Back Syndrome, Radicular Pain Syndrome, Radiculopathy, Herniated Disc, Secondary FBS, Postlaminectomy Pain, Multiple back operations, Unsuccessful disc surgery, Peripheral causalgia, Epidural Fibrosis, Arachnoiditis, Lumbar Adhesive arachnoiditis, Complex regional pain, and Reflex sympathetic dystrophy and

Painful Diabetic Neuropathy among pediatric subpopulations. The search resulted in 254 articles, 43 of which qualified for full text review. Of the 43 articles which qualified for full-text review, 6 articles qualified for summarization. Articles were excluded for reasons such as study population greater than 21, lack of pediatric subpopulation analysis, reliance on only case reports, inclusion of a non-US population, non-systematic review, etc.

The analysis was divided into three general categories, including Failed Back Surgery Syndrome (FBSS) and degenerative spine conditions, Complex Regional Pain Syndrome (CRPS), or Painful Diabetic Neuropathy (PDN). Each of the conditions mentioned in the literature search above fall into one of these categories.

FBSS causes instability or pain in patients who have undergone multiple lumbosacral spine surgeries. Fibrosis and degenerative disc diseases refractory to surgical intervention result in radiculopathies and continued pain. These conditions may progress to a neuropathic state. In a systematic review published by Hurwitz et al., two studies reported the prevalence of back pain reported by individuals ≤ 21 years of age ranging from 11.4% to 15.9% in Chinese and Ethiopian populations.[44]

CRPS or causalgia typically occurs after injury or surgery. Incidence of CRPS ranged from 1.16 to 50 per 100,000 in Children and Adolescents respectively. A report by Elsharydah et al. cites that while CPRS occurs in patients 18 and older, it is more common in the 5th to 7th decade of life.[45]

Patients with PDN suffer from prickling, aching, burning pain with intermittent sharp stabbing electric shock-like pains which begin in the feet, spreading to the lower legs and upper limbs. Some patients also present with possible sensory abnormalities when in contact with clothing or bedding. Jaiswal et al. described that the prevalence of diabetic peripheral neuropathy was 7% in pediatric patients with type 1 diabetes and 22% in pediatric patients with type 2 diabetes.[46]

Medtronic SCS systems are generally used in older individuals rather than pediatric patients. This is because chronic pain of the trunk and/or limbs is most often seen in older patient populations. Chronic back and leg pain associated with FBSS or other degenerative spine conditions are almost exclusively diagnosed in older populations. CRPS and PDN occur in pediatric populations but are more frequently seen in populations over 40 years old. However, Eichholz et al. observed that African American and Hispanic populations with diabetic neuropathy contain a greater proportion of younger individuals.[47]

E. Financial Disclosure

A clinical study was not performed and thus, the Financial Disclosure by Clinical Investigators regulation (21 CFR 54) is not applicable to this PMA.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurology Review Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

A total of 12 publications from 6 prospective studies (several publications reported alternative analyses or long-term follow-up) described effectiveness outcomes associated with SCS to treat PDN. Four prospective studies without a comparator included a total of 48 subjects. Two RCTs comparing SCS to the standard-of-care included a total of 96 subjects.

Two similar, independent RCTs evaluating SCS to treat PDN compared to standard-of-care included a total of 62 subjects in the treatment group and 34 subjects in the control group. At the 6-month primary endpoint, the outcomes for subjects randomized to receive SCS treatment were consistent between both studies with treatment success rates of 59% and 63% and an average pain relief of 44% and 58% for Slangen et al. (2014) and de Vos et al. (2014), respectively. Data pooled from both studies showed a probability of treatment success for all subjects randomized to receive SCS treatment of 61% and for implanted subjects of 70%, along with an average pain relief of 53%. A meta-analysis of both studies comparing treatment with SCS versus the control group resulted in an OR for treatment success of 17.4. Two independent meta-analyses drew similar conclusions in terms of pooled results. One meta-analysis pooled EQ-5D results and reported a significant mean difference between treatment and control groups, reflecting a significant improvement in subject health status with SCS treatment. Data on subjects treated with SCS to treat PDN from one non-randomized study and one RCT reflecting outcomes after 5 years of treatment showed a sustained pain relief at clinically meaningful levels.

Limitations of the available data include lack of a placebo control in the 2 randomized studies, no impact of medication use on criteria for treatment success, and the open-label design of long-term follow-up reports. Studies without a placebo control arm are unable to measure the contribution of the placebo effect to the overall outcomes reported by subjects. While study data may reflect an average reduction in medication use, an individual patient's treatment success with SCS could be attributed to changes in pain medication. Data from open-label studies or long-term non-randomized follow-up may result in an overestimation of

the treatment effect.

The data from these studies support the effectiveness of a Medtronic implantable neurostimulation system for treating patients who suffer from chronic, intractable pain of the trunk and/or limbs, including PDPN of the lower extremities.

B Safety Conclusions

The clinical evidence supporting the safety of Medtronic implantable neurostimulation systems to treat PDN includes a systematic literature review of published scientific literature reporting SCS to treat chronic intractable pain in patients with diabetes in general, and primary source (patient-level) data from the Medtronic PSR on patients treated with SCS to treat PDN. Safety data from 288 subjects treated with SCS for their PDN was included. An additional 2,233 patients were included across 4 studies which reported on diabetic patients treated with SCS, with 3 focusing on infection rates. With the exception of infection, the rates of common adverse events in the PDN population were similar to that of the general SCS population. Published literature describing SCS to treat PDN and published clinical practice guidelines on peri-operative care of diabetic patients provide information on specific inherent risks for the diabetic patient in the delivery and management of SCS therapy. These incremental risks include, but are not limited to, infection, delayed wound healing, cardiovascular events, dural puncture and subsequent subdural hematoma, and fluctuations in glycemic control. These events may be avoided by appropriate patient selection.

Limitations of data on the safety of SCS to treat PDN based on published literature is the lack of access to primary source data on patient-reported outcomes such as detailed adverse event descriptions. Variation in diagnosis descriptions and criteria for inclusion of adverse events reported in publications limits the resolution of safety information that can be extracted from the published literature.

Underlying health conditions related to diabetes or other diseases may disqualify some patients from receiving SCS. Labeling (Information for Prescribers) has been updated to include added safety information specifically addressing the diabetic population.

C. Benefit-Risk Determination

Treatment of the underlying diabetes, if possible, is generally the primary approach to pain management. Pharmacologic treatments are delivered to address the symptoms of pain. Non-pharmacologic treatments (physical therapy, cognitive therapy, and TENS) should be provided in conjunction with first-line medical

treatment. Given the considerable and growing population with diabetes, a significant number of people likely remain undertreated and without alternatives for relief.

The benefits of SCS to treat PDN observed in randomized trials reflected treatment success, defined by multiple measures, in 70% of implanted subjects. Pain relief was reduced by ≥50% in 63% of implanted subjects, and the average reduction in pain score was 53%. Two independent meta-analyses provided consistent results with this reflection of pooled data and reported significant improvements in subject health status (EQ-5D). Long-term treatment success at 5 years was demonstrated in a study of subjects pooled from a single-arm cohort and an RCT. Treatment success was sustained in 65% of subjects at two years and in 55% of subjects at 5 years. These benefits represent meaningful improvements in the chronic intractable pain associated with PDN that are sustained in the long-term.

An assessment of practice guidelines on the perioperative care of diabetic patients provided specific complications to which the diabetic patient is predisposes as well as precautions to take to avoid or minimize the increase impact of these complications. The analysis of the adverse event profile of the use of SCS to treat PDN showed common adverse event rates were in the ranges reported for the general population of SCS patients, with two notable differences. While three studies examining the association of infection related to the treatment of pain with SCS showed no significant impact of diabetes, an analysis of infection comparing PDN and non-PDN patients in the PSR showed a significant rate of infection. Also noted was the potential for blood glucose to fluctuate in response to an adverse event. Diabetic patients may more frequently have cardiovascular diseases, autonomic neuropathy, renal disease, or other comorbid conditions. Device labeling has been updated to provide information on warnings, advice on appropriate selection of patients healthy enough for an SCS procedure, and steps to take to avoid or reduce the impact of complications with SCS.

Beyond management of glycemic control, only palliative treatments are available. For intractable pain as a result of PDN, patients have few options after medical management. No disease-modifying intervention beyond medications is available to treat PDN. In two well designed and executed randomized studies comparing SCS to treat PDN to conventional medical management, most subjects experienced clinically meaningful reduction in pain symptoms, and those that do experience relief generally do so beyond the primary endpoints of the studies. In a thorough review of available data on the risk profile of the therapy in PDN patients, the adverse event profile of the therapy was consistent with general population overall, with exceptions of infection and glycemic control. This does not eliminate the known higher relative risks for surgical complications in diabetic patients. Relative to the lack of treatment alternatives, for well selected, well monitored patients with sufficient glycemic control, SCS offers an acceptable option for the treatment of intractable PDN where the benefits outweigh the risks associated with the therapy.

1. Patient Perspective

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for a Medtronic implantable neurostimulation system when used as an aid in the management of chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain associated with PDPN of the lower extremities.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the instructions for use.

Beyond management of glycemic control, only palliative treatments are available to treat PDPN. For intractable pain as a result of PDPN, patients have few options after medical management. In two well-designed and executed randomized studies comparing SCS to treat PDN to the standard-of-care, most subjects experienced clinically meaningful reduction in pain symptoms, and most do so beyond the primary endpoints of the studies. In a thorough review of available data on the risk profile of the therapy in PDN patients the adverse event profile of the therapy was consistent with that of the general population treated with SCS overall, with the exception of an increased infection rate and exacerbation of unstable blood glucose levels if an adverse event were to be experienced. Underlying conditions and inherent surgical risks for diabetic patients required additional consideration when selecting patients healthy enough for an SCS procedure. Relative to the lack of treatment alternatives, for patients without contraindications, SCS offers an option for the treatment of intractable PDPN where the benefits outweigh the risks associated with the therapy.

XIII. CDRH DECISION

CDRH issued an approval order on January 24, 2022.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.
Post-approval Requirements and Restrictions: See approval order.

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