SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: Precision™ Spinal Cord Stimulator System
Precision Spectra™ Spinal Cord Stimulator System
Precision Novi™ Spinal Cord Stimulator System
Precision™ Montage™ MRI Spinal Cord Stimulator System
Precision™ Montage™ Spinal Cord Stimulator System
Spectra WaveWriter™ Spinal Cord Stimulator System
WaveWriter Alpha™ Spinal Cord Stimulator System
WaveWriter Alpha™ Prime Spinal Cord Stimulator System

Device Procode: LGW, QRB

Applicant's Name and Address: Boston Scientific Neuromodulation Corporation
25155 Rye Canyon Loop
Valencia, CA 91355

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P030017/S357

Date of FDA Notice of Approval: 10/05/1023

The original PMA P030017 was approved on April 27, 2004 and is indicated 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: failed back surgery syndrome, intractable low back pain and leg pain. PMA Supplement S275 was subsequently approved to add the following associated conditions and etiologies: radicular pain syndrome, radiculopathies resulting in pain secondary to failed back syndrome or herniated disc, epidural fibrosis, degenerative disc disease (herniated disc pain refractory to conservative and surgical interventions), arachnoiditis, and multiple back surgeries. The SSEDs to support those indications are available on the CDRH website. The current supplement was submitted to expand the indication for the Boston Scientific Spinal Cord Stimulator Systems to add diabetic peripheral neuropathy (DPN) of the lower extremities for paresthesia-based stimulation only.

II. INDICATIONS FOR USE

The Boston Scientific Spinal Cord Stimulator Systems are indicated 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:

- Failed Back Surgery Syndrome,
- Complex Regional Pain Syndrome (CRPS) Types I and II,

- Diabetic peripheral neuropathy of the lower extremities,
- Intractable low back pain and leg pain,
- radicular pain syndrome,
- radiculopathies resulting in pain secondary to failed back syndrome or herniated disc,
- epidural fibrosis,
- degenerative disc disease (herniated disc pain refractory to conservative and surgical interventions),
- arachnoiditis,
- multiple back surgeries.

III. CONTRAINDICATIONS

The following patients are contraindicated from being treated with Boston Scientific Spinal Cord Stimulator Systems:

- Poor surgical candidates;
- Unable to operate the SCS system;
- Failed trial stimulation by failing to receive effective pain relief;
- Pregnant.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Boston Scientific Spinal Cord Stimulator Systems labeling.

V. DEVICE DESCRIPTION

Boston Scientific Spinal Cord Stimulator (SCS) Systems are totally implanted devices that deliver electrical stimulation to the dorsal column of the spinal cord for the treatment

of chronic intractable pain of the trunk and/or limbs. Figures 1 and 2 display main system components and the typical location of implanted components.

Figure 1: The Boston Scientific Spinal Cord Stimulation System

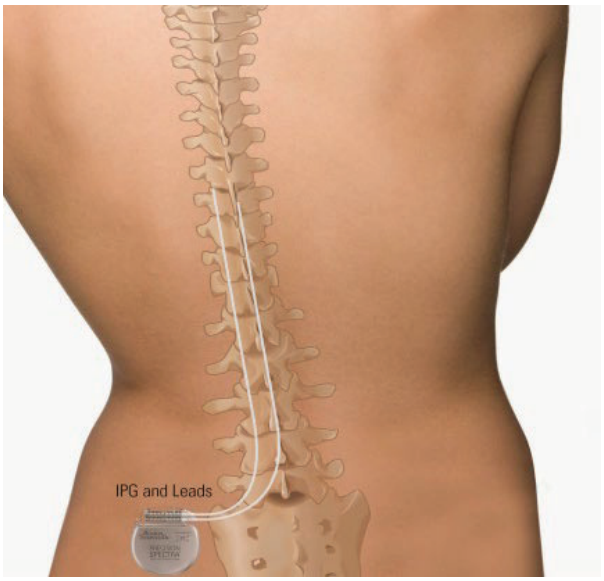

Figure 2: Typical location of implanted pulse generator and percutaneous leads.

A. Implanted Components

The implanted components of the Boston Scientific SCS System include the following:

- Implanted Pulse Generator (IPG): Generates programmable electrical pulses that are conducted to the spinal cord via leads. Includes rechargeable or non-rechargeable batteries.
    - IPG models include Precision, Precision Spectra, Precision Novi, Spectra Wavewriter, Precision Montage, Precision Montage MRI, WaverWriter Alpha and WaveWriter Alpha Prime.
- Percutaneous and Surgical Leads: Available in various lengths and configurations, the leads are connected to the IPG to deliver stimulation to the spinal cord.
    - Percutaneous lead models include Linear, Linear ST, Linear 3-4, Linear 3-6, Infinion, Infinion CX and Avista MRI.
    - Surgical lead models include CoverEdge, CoverEdge X and Artisan.
- Lead Extension: Lead Extensions are designed to provide additional length to connect the leads to the stimulator. Lead extensions come in lengths of 25cm, 35cm, and 55cm.

- Lead Splitters: Optional component used to connect multiple leads to the IPG.

- Implantable Adaptors: Adaptors are provided to connect other manufacturer's leads to Boston Scientific IPGs (e.g., Model M8 adaptor allows IPGs to be connected to Medtronic leads and Model S8 allows IPGs to be connected to St. Jude leads).

- Suture Sleeves and Anchors: Used to anchor the lead to the supraspinous ligament or deep fascia.

B. External Components

The external components of the Boston Scientific SCS System include the following:

- External Trial Stimulator (ETS): The ETS is intended to provide trial stimulation with implanted leads before permanent placement of the IPG. It provides the identical stimulation capabilities as the IPG.

    - ETS models are the Precision ETS, Precision Spectra ETS and the WaveWriter Alpha ETS.

- Clinician Programmer (CP): The CP installed with the Bionic Navigator programming software is used by the clinician to program the IPG and ETS, and thus prescribe stimulation therapy for the patient.

- Remote Control (RC): The Remote Control is a hand-held, battery operated unit that uses telemetry to communicate with the IPG and ETS. It allows the patient to control the stimulation therapy prescribed by the clinician (e.g., turn SCS system on and off).

    - RC models are the Precision RC and the FreeLink RC.

- Programming Wand: The programming wand is used with some systems to allow the CP to communicate wirelessly with the IPG and ETS.

- Charger: The Charger is used with all rechargeable IPGs to transcutaneously charge the IPG battery.

C. Accessories

Accessories provided with the Boston Scientific SCS Systems include the following:

- Torque Wrench: Used to tighten the set screws that lock the lead into the IPG.

- Stylets: Used to maneuver the lead through the epidural space to the desired implant location.

- IPG Template: guides the physician to create the correct sizing of the subcutaneous pocket.

- Insertion Needle: used during implant procedure to introduce the percutaneous lead into the epidural space.

- Lead Blank: optionally used during implant procedure to clear a path for the introduction of the lead into the epidural space.

- Tunneling Tool: Used to create a subcutaneous tunnel from the IPG site to the lead implant location.

- IPG Connector Plug/Port Plug: Provided to seal the port(s) of the IPG that are not in use.

- OR (Operating Room) Cable and Extension: Used to connect the lead to the ETS during intraoperative testing and trial phase.

- External Adaptors: For connecting other manufacturer's SCS leads to the Boston Scientific external stimulators during in-office evaluation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of chronic intractable pain of the trunk and/or limbs. Patients are typically treated on a treatment continuum with less invasive therapies prescribed first. Established non-surgical treatment options include, but are not limited to: oral medications (including Non-Steroidal Anti-inflammatory Drugs and opioids), massage therapy, physical/occupational/exercise therapy, psychological therapies (e.g., behavior modification, hypnosis), Transcutaneous Electrical Nerve Stimulation (TENS), acupuncture, sympathetic nerve blocks, epidural blocks, intrathecal blocks, and facet joint blocks. The surgical treatment options for these patients include sympathectomy, implantable intrathecal drug delivery systems, partially implanted SCS systems (power source is external) and commercially available fully implantable SCS systems.

There are several other alternatives for the treatment of chronic, intractable pain associated with DPN of the lower extremities. Treatment of DPN 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

Currently, the Boston Scientific Spinal Cord Stimulator System is commercially distributed in the United States, European Community (EC) countries, Canada, Australia/New Zealand, Brazil, Kuwait, Israel, Japan, Argentina, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Mexico, Panama, Peru, El Salvador, Russia, Belarus, Algeria, Georgia, Iran, Iraq, Jordan, Kuwait, Kazkhastan, Lebanon, Pakistan, Qatar, Saudi Arabia, South Africa, Turkey, Ukraine, China, Singapore and United Arab Emirates.

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 SCS Systems. The Boston Scientific SCS systems are similar to other legally-marketed SCS systems in intended use, target patient population, technology, device design and output characteristics. Therefore, the following list of potential adverse effects have been identified from peer-reviewed published literature that describes studies of all legally-marketed SCS systems.

The adverse effects include: (1) those associated with any surgical procedure, (2) those associated with the SCS system placement procedures, and (3) those associated with having an implanted SCS system to treat pain, including the Boston Scientific SCS System. In addition to the risks listed below, there is the risk that the SCS therapy may not be effective in relieving symptoms, or may cause worsening of symptoms. Additional intervention may be required to correct some of the adverse effects.

- Risks associated with any surgical procedure: abscess; cellulitis; excessive fibrotic tissue; wound dehiscence; wound, local or systemic infection; wound necrosis; edema; inflammation; foreign body reaction; hematoma; seroma; thrombosis; ischemia; embolism; thromboembolism; hemorrhage; thrombophlebitis; adverse reactions to anesthesia; hypertension; pulmonary complications; organ, nerve or muscular damage; gastrointestinal or genitourinary compromise; seizure, convulsion, or changes to mental status; inability to resume activities of daily living; and death.

- Risks associated with SCS system placement procedures: temporary pain at the implant site, infection, cerebrospinal fluid (CSF) leakage, CSF fistula, epidural hemorrhage, bacterial meningitis, seroma, hematoma, and paralysis. Patient use of anticoagulation therapies may increase the risk of procedure-related complications such as hematomas, which could produce paralysis.

- Risks associated with the use of a SCS system: lead migration; IPG migration; allergic response or tissue reaction to the implanted system material; hematoma or seroma at the implant site; skin erosion at the implant site; persistent pain at the IPG, extension, or lead site; radicular chest wall stimulation; disturbed urination; dysesthesia; decubitus; premature battery depletion; loss of pain relief over time; and uncomfortable stimulation or ineffective pain control caused by random failure of the system components or battery, changes in electrode position, loose electrical connections, lead or extension insulation breaches or fractures; and changes in blood glucose levels.

- For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Pre-clinical studies (bench and animal) previously submitted to FDA in the Original PMA application (P030017) and supplements continue to support the safety of the commercially available Boston Scientific SCS System for treatment of chronic intractable pain of the trunk and/or limbs. No additional preclinical studies were required to evaluate the safety of Boston Scientific SCS therapy for the treatment of the new patient populations. The previously approved supplements which support the device and its components are listed below:

System/Device Component	Approval Reference
Precision™ Spinal Cord Stimulator System Includes IPG, Linear Leads, Lead Extensions, External Trial Stimulator, Remote Control, Charger, Base Station, Clinician Programmer	P030017
Artisan Leads	P030017/S008
Linear ST Leads	P030017/S020
Connector M1	P030017/S025
Linear 3-4 and Linear 3-6 Leads	P030017/S100
Infinion Leads	P030017/S119
Infinion CX Leads	P030017/S191
Precision Spectra™ Spinal Cord Stimulator System Includes IPG, FreeLink Remote Control, External Trial Stimulator, Programming Wand, Clinician Programmer	P030017/S134
CoverEdge Leads	P030017/S152
M8 Adapter	P030017/S202
S8 Adapter	P030017/S210
Precision Novi™ Spinal Cord Stimulator System	P030017/S217

Precision™ Montage™ MRI Spinal Cord Stimulator System Includes Avista MRI leads	P030017/S235
Precision™ Montage™ Spinal Cord Stimulator System	P030017/S235
Spectra WaveWriter™ Spinal Cord Stimulator System	P030017/S271
WaveWriter Alpha and WaveWriter Alpha Prime Spinal Cord Stimulator Systems	P030017/S338

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The Boston Scientific SCS Systems were previously approved 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: failed back surgery syndrome, intractable low back pain and leg pain. The safety and effectiveness of Boston Scientific SCS Systems have been previously established for indicated patients suffering from a variety of conditions (see Section I).

The clinical evidence to support safety and effective use of the Boston Scientific SCS Systems in the diabetic peripheral 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).

The Boston Scientific SCS Systems are similar in design, technology, performance, and intended use to the SCS systems used to treat the patient populations in the submitted published clinical studies for paresthesia-based stimulation only. Where reported, the stimulation parameters and capabilities used by SCS devices in these studies are aligned with the range of parameters approved for Boston Scientific SCS devices. Therefore, data obtained from these published studies were used to establish a reasonable assurance of safety and effectiveness of the paresthesia-based stimulation mode for Boston Scientific SCS Systems for use in the diabetic peripheral neuropathy population.

Additional clinical evidence for safety was obtained from a cohort of DPN patients identified in the Boston Scientific RELIEF Registry Study, who were treated for chronic pain due to diabetic peripheral neuropathy.

The data obtained from the published studies, along with data from the Boston Scientific RELIEF Study were the basis for the PMA approval decision.

X.1 Literature Review

A. Study Design

A systematic review of published literature was conducted by searching PubMed for terms relating to SCS and diabetes. The Boston Scientific SCS Systems are similar to the SCS systems reported in the published literature in intended use, device design, and output characteristics. Based on these similarities, the primary objective of the literature search was to provide clinical evidence of the effectiveness of SCS Systems when they are used to treat patients with painful diabetic neuropathy (PDN). PDN encompasses

many different types of neuropathy, including painful diabetic peripheral neuropathy (PDPN), autonomic neuropathy, proximal neuropathy, and mononeuropathy.

21 articles were included for literature analysis of SCS for the treatment of PDPN. Of the 21 publications, 15 were of prospective studies, including two randomized controlled trial (RCT) studies (de Vos et al., 2014b; Slangen et al., 2014) that compared the 'SCS plus medication' with the 'medication alone' to treat PDN or PDPN. 6 studies were of retrospective design, which were included for safety data of the diabetic patients only. These retrospective studies analyzed the likelihood of the diabetic condition being one of the risk factors for various safety outcomes.

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. Effectiveness data was extracted from all publications, if available, and included in total for each cohort. Publications were excluded from effectiveness analysis if the diabetic condition treated was not specific to PDN or if the devices used were not equivalent to Boston Scientific SCS devices. Out of the 21 publications, 11 publications (6 cohort studies) were used for effectiveness analysis and 16 publications were used for safety analysis. The study follow-up times ranged from 2 weeks to 7 years.

The effectiveness measures used in the studies' data analyses included the following:

- Overall pain or pain intensity scales: Visual Analog Scale (VAS), Numeric Rating Scale (NRS), McGill Pain Questionnaire (MPQ) or short form McGill Pain Questionnaire (SF-MPQ), and Neuropathic Pain Scale (NPS).
- Measures of improvement: Patient Global Impression of Change (PGIC) questionnaire.
- Quality of life: EuroQoL 5D form (EQ-5D), Quality-adjusted Life Years (QALY), MPQ-QoL, and Medical Outcomes Study SF-36 (MOS-SF-36).
- Sleep and mood: Medical Outcomes Study Sleep Scale (MOS-SS) and Becks' Depression Inventory (BDI).
- Pain disability scales: Pain Disability Index (PDI) and modified Brief Pain Inventory- Diabetic Peripheral Neuropathy (mBPI-DPN).
- Medication Use: Medication Quantification Scale (MQS III).

B. Literature Search Strategy

Databases searched: PubMed (available through National Center for Biotechnology Information [NCBI] at the National Library of Medicine [NLM] located at the National Institute of Health [NIH]. It was accessed at the website:
https://pubmed.ncbi.nlm.nih.gov
Search terms: (diabetes) AND ("spinal cord stimulation")
Filters applied: Human, English

- Inclusion criteria:

  For safety of SCS to treat PDN –

- Report reflected the experience of patients treated with SCS for any condition where a diagnosis of diabetes was considered.
- 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.

For effectiveness of SCS to treat PDPN –

- Publication must include data from prospective studies on SCS to treat PDPN 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.

- Exclusion criteria:

  For effectiveness of SCS to treat PDPN –

  - Any SCS studies that did not include PDPN patients
  - All devices used in the study provide treatment that is not equivalent to BSC SCS devices, e.g. treatment with 10 kHz SCS, or transcutaneous SCS.
  - Results not associated with pain improvement

For safety data, an attempt was made to use only data applying to PDN or PDPN. However, if separation was impossible, a conservative method was applied such that the safety events potentially related to SCS treatment of PDN were included.

C. Safety and Effectiveness Results

1. Safety Results

Published literature evaluating 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. Sixteen (16) of the 21 articles, representing 11 studies, contained sufficient reports on adverse events (AEs) for the safety analysis. AE counts and patient populations were confined to diabetic patients or subjects exposed to SCS (at least an SCS trial) whenever possible. Safety data from 300 subjects treated with SCS for their PDN was included. An additional 2,235 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.

Table 1 provides a summary of Adverse Events (AEs) reported in the 16 publications included in the safety analysis. An AE was counted if a) the article stated it was related to device or procedure, or b) the event has a potential relationship to the device or procedure.

Table 1: Adverse Events Detail by Study

	Primary Author	**N[a]**	**Reported Adverse Events (AEs)** *Related or possibly-related to SCS stimulation, device, or procedure*	**Adverse Events Coded into Common Terms**
PDN	Tesfaye (1996) Daousi (2005)	10	• 2 superficial infections, treated with antibiotics • 1 hematoma at implant site without clinical impact • 2 lead migration with revision • 1 lead failure due to trauma, replaced • 1 skin peeling at transmitter site upon removal of the adhesive patch	2 Infection 1 Hematoma/Erosion/Wound 2 Lead Migration 1 Lead Failure 1 Other
	de Vos (2009)	11	• 2 lead/extension failures with revisions • 1 mild infection treated with antibiotics	2 Lead Failure 1 Infection
	de Vos (2014b)	40	Procedure related adverse events: • 2 pain at IPG implant site, resolved by device repositioning • 2 required additional lead placed to cover painful area • 1 lead migration with revision • 1 infection during trial period • 1 coagulopathy resulting in prolonged hospitalization	2 Device Site Swelling or Pain 2 Uncomfortable Stimulation/ Stimulation Issue 1 Lead Migration 1 Infection 1 Other
	Pluijms (2012), Slangen (2013), Slangen (2014), van Beek (2015), van Beek (2018)	49	• 10 subjects reporting pocket pain with 1 leading to revision due to persistent pain, without complete resolution of pain • 9 subjects reporting uncomfortable stimulation • 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	10 Device Site Swelling or Pain 9 Uncomfortable Stimulation/ Stimulation Issue 5 Lead Migration 4 Lead Failure 2 Infection 1 CSF Leak
	Galan (2020)	9	• 1 pain in extremity (left leg) • 1 implant site seroma • 1 wound dehiscence	1 Other 1 Device Site Swelling or Pain 1 Hematoma/Erosion/Wound

* Sample size reflects diabetic patients or subjects exposed to SCS (at least an SCS trial) as described in the individual reports.

	Primary Author	N[a]	Reported Adverse Events (AEs) *Related or possibly-related to SCS stimulation, device, or procedure*	Adverse Events Coded into Common Terms
	Petersen (2021, 2022)	181	• 3 infection • 2 wound dehiscence • 1 impaired healing • 1 device extrusion • 1 incision site pain • 1 IPG discomfort • 1 lead migration • 1 contact dermatitis • 1 utricaria • 1 radiculopathy • 1 uncomfortable stimulation • 1 gastroesophageal reflux • 1 myalgia • 1 arthralgia • 1 hyporeflexia • 8 infection (5 requiring explant) • 2 IPG location revision • 1 lead migration with revision	3+8 Infection 4 Hematoma/Erosion/Wound 2+2 Device Site Swelling or Pain 1+1 Lead Migration 1 Uncomfortable Stimulation/ Stimulation Issue 7 Other
General Diabetes	Petrakis (1999)	64	• 2 infections requiring explant • 2 lead migrations with revision	2 Infection 2 Lead Migration
	Mekhail (2011)	56	• 5 infections requiring explant	5 Infection
	Hoelzer (2017)	452	• 9 infections	9 Infection
	Falowoski (2019)	1663	• 59 infections	59 Infection

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

Overall, the safety profile of SCS use in diabetic populations is similar to that observed in non-diabetic patients in most reports, with some exceptions. 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.

Clinical practice guidelines on the perioperative care of diabetic patients

Diabetes has been identified as an important risk factor for complications in general for some surgical conditions. Recommendations on the perioperative care of diabetic patients are summarized in Table 2 below. 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 (OR) 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% (Marchant et al. 2009). 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; $p < 0.001$; Marchant et al. 2009). Slangen et al. (2014) reported one subject death following a dural puncture and subsequent CSF leak leading to a cranial subdural hematoma. Ha et al. (2016) reported data from craniotomy procedures concluding that diabetic patients may be at higher risk of CSF leak (Univariate regression model; $p = 0.021$). Though a Multivariate regression model did not find significant relation between diabetes and CSF leak (Odds Ratio = 1.82; $p = 0.448$). 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, $p < 0.0001$). 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.

Table 2: Clinical Guidelines on Perioperative Care of Diabetic Patients

Author and Title	Summary	Recommendations	Noted Complications
Berhe et al. **Intl. J. Surg. 2017** **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** **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** **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 closely to avoid hyperglycemia	• Infections • Delayed wound healing • Increased morbidity and mortality
Cheisson et al. **Anaesthesia, critical care & pain medicine. 2018** **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** **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** **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
Mumdzic & Munir, **Surgery. 2020** **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** **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
Simha & Shah. **JAMA. 2019** **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

Author and Title	Summary	Recommendations	Noted Complications
Stryker. **The Journal of Arthroplasty. 2016** **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 • 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	• Delayed wound healing • Deep infection • Thrombosis • Mortality
Wang et al. **Clinical neurology and neurosurgery. 2021** **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

Table 3: 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), 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), 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), Lumbar fusion surgery, Infection rate 0.68%	Brown et al. (2007), OR = 1.52
	Anderson et al. (2017), Spine surgery, Infection rate for highest risk groups undergoing laminectomy = 2.3%	Anderson et al. (2017), OR = 2.04
	Marchant et al. (2009), 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), hemodynamic instability**	Marchant et al. (2009), Total Joint Arthroplasty, Myocardial infarction = 0.01%; Stroke = 0.2%	Marchant et al. (2009) , Myocardial infarction OR = 1.54 in uncontrolled diabetics (p>0.05); Stroke OR = 3.42
CSF leak-subdural hematoma	Wang et al. (2014), 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), 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), SCS to treat PDN, Rate of glucose fluctuation in diabetic patients subsequent to an infection = 5%	N/A - Experienced only by diabetics

2. Effectiveness Results

Results from Randomized Controlled Trials (RCT)

Two RCT studies investigating the use of SCS to treat PDN were described across 4 publications (Slangen et al. 2014, van Beek et al. 2015, de Vos et al. 2014b, and Duarte et al. 2016). The details of these two studies are summarized in Table 4.

Table 4: Details of Publications Describing RCT Studies on PDN

Publication	**Slangen et al. 2014**	**de Vos et al. 2014b**
Sponsor	Maastricht University Medical Center (Clinicaltrials.gov: NCT01162993)	Medisch Spectrum Twente (Dutch Trial Register: ISRCTN03269533)
Population	• Diabetes Mellitus patients suffering from moderate to severe painful diabetic peripheral neuropathy in the lower limbs refractory to conventional treatments for more than 12 months • Reporting an NRS ≥ 5 • Between 18 and 80 years of age	• Patients suffering from diabetic neuropathic pain in the lower extremities for more than 1 year • Refractory to conventional pain 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)	Conventional medical practice (CMP)
Sample size (countries)	36 from 2 centers (NL) SCS+BMT group: 22; BMT group: 14	60 from 7 centers (NL, BE, DK, DE) SCS+CMP group: 40; CMP group: 20
Primary endpoint	Treatment success at 6 months: ≥ 50% pain reduction for 4 days during daytime or nighttime or a score of ≥ 6 on a 7- point PGIC Likert scale for pain and sleep	Treatment success at 6 months: ≥ 50% pain reduction
Effectiveness Measures	NRS, PGIC (pain and sleep), EQ-5D, mBPI-DPN, NPS, MOS SF-36, MOS Sleep Scale, depression (BDI), Medication Use	VAS, SF-MPQ, PGIC, EQ VAS, MQS III, EQ-5D, QALY* **QALY is calculated and published in Duarte et al., 2016.*

The demographic characteristics of subjects in both studies were similar for age, duration of disease (diabetes and DPN), and gender. Fewer Type I diabetic subjects were included in Slangen et al. (2014) although in both studies the majority of subjects were diagnosed as Type II diabetics. Subject demographics for each study are presented in Table 5.

Table 5: Comparison of Study Demographics

Demographic	Slangen et al. 2014	de Vos et al. 2014b
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 6. Pain-related outcomes were similar between studies with slightly greater reductions in pain reported by de Vos et al. Neither control groups achieved sufficient reduction in average pain; however, one subject in the control arm reported treatment success (de Vos et al., 2014b).

Table 6: Comparison of Pain Measures

Pain Rating [a]	Slangen et al. 2014		de Vos et al. 2014b	
	SCS (n=22)	Control (n=14)	SCS (n=40)	Control (n=20)
Baseline	Day 7.1 ± 1.7 Night 6.3 ± 2.5	Day 6.5 ± 1.7 Night 7.3 ± 1.8	7.3 ± 1.6	6.7 ± 1.8
6-month	Day 4.0 ± 2.9 [c] Night 3.9 ± 3.1 [c]	Day 6.5 ± 1.9 Night 6.4 ± 2.1	3.1 ± 2.8	6.7 ± 2.1
Pain Relief	Day 44% Night 38%	Day 0% Night 12%	58%	0%
Responder Rate [b]	59%	7%	63%	5%

a. VAS (0-100 mm) and NRS (0-10) were normalized to a 0-10 scale
b. Study design defined successful pain relief by different measures (see Table 4)
c. n=19 subjects with available data for pain scores at 6-months

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 (i.e., conventional management) with a primary endpoint at 6 months of follow-up. Data from both studies were pooled and are presented in Table 7. Average values were weighted by the number of subjects in the respective SCS and Control treatment groups for each study.

Table 7: 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 [a]	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 [b]	53%	0%
Responder Rate per protocol [c,d]	61% (48%-73%)	6% (0%-20%)
Responder Rate ≥ 50% reduction in pain [d]	55% (42%-68%)	3% (0%-15%)
Responder Rate per protocol as-treated [e]	70% (56%-82%)	6% (0%-20%)
Responder Rate ≥ 50% reduction in pain as-treated [e]	63% (49%-76%)	3% (0%-15%)

a. Baseline pain rating is based on the daytime pain score from Slangen et al. 2014 and the average pain score from de Vos et al. 2014b.
b. Confidence interval for the percent mean change have not been calculated because biased due to the percent asymmetry
c. Each study design defined successful pain relief by different measures (see Table 4)
d. Analysis of all randomized subjects in an intent-to-treat approach
e. Including only subjects who received an SCS system implant

Two publications (Raghu et al., 2021 and Duarte et al. 2021) reported meta-analyses of these two RCT studies of SCS to treat DPN. An analysis of heterogeneity between the studies supported homogenization (Cochran's Q=0.658, $p = 0.419$; Higgin's I2 test < 0). The confidence intervals of these studies overlap and the estimate of Odds Ratios (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). After 2 years, 65% of subjects were reported as treatment success.

EQ-5D scores were significantly improved through 24-months. Seventy-nine percent (79%) 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). Forty-eight (48) subjects were included in the analysis (40 with permanent implant) 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.

Effectiveness results from all publications

Besides the 2 RCT studies and associated publications detailed above, 6 publications included data on 4 prospective single-arm studies of SCS to treat PDN (Tesfaye et al. 1996, Daousi et al. 2005, de Vos et al. 2009, de Vos et al., 2014a, Pluijms et al. 2012, and Slangen et al. 2013).

The effectiveness data from the 4 prospective single-arm studies representing 44 subjects are summarized in Table 8 along with the data from the 2 RCT studies.

All combined, these results show effectiveness for SCS to treat pain in the DPN population, and the effectiveness continued for both short and long-term follow-ups.

Table 8: Pain-Specific Measures

Primary Author	Study Type	Diagnosis	# of Subjects at Baseline / at Last Follow-up	Outcomes
Tesfaye (1996)	Prospective, non-comparative	Chronic Painful Diabetic Neuropathy (excluding neuropathic pain in upper limbs)	Enrolled 10 Baseline 8 3 mo: 7 6 mo: 7 14 mo: 7	**Pain Relief (Stimulation ON vs. OFF)** Statistically significant relief of both background and peak pain was achieved. 3 mo: 57% background, 34% peak ($p = 0.016$), 6 mo: 58% background, 59% peak ($p = 0.03$), 14 mo: 70% background ($p = 0.06$), 75% peak ($p = 0.03$). 60% (6/10 of subjects ≥ 50% pain relief with continued SCS use at last follow-up (14 months).
Daousi (2005)			3 yr: 6 7 yr: 4	**Pain Relief (Stimulation ON vs. OFF)** Background and peak pain relief: 3 yr: 66% background, 78% peak ($p = 0.03$). 7 yr: 55% background, 51% peak ($p = 0.06$). At 7 years, all 4 patients continued to report at least 50% relief of their background and peak pain. **Disability** All 4 patients at last follow up reported ≥ 50% improvement in their performance in the 6 areas of the PDI. **Medication use** At 3 and 7 years, all surviving patients reported a reduced analgesic intake compared with before the SCS implant. At 3 and 7 years, 3 and 2 patients, respectively, were not taking any regular analgesics.
de Vos (2009)	Prospective, non-comparative	Peripheral Diabetic Neuropathy (pain in lower limbs)	Enrolled 11 Baseline 9 1-12 mo: 9 30 mo: 8	**Pain Relief** At last follow-up of 30 months: Pain relief was 70%, p value: NR. 64% (7/11) patients had ≥ 50% pain relief. 75% (6/8) patients had PGIC- 'very much improved' or 'much improved'. **Medication use** 8 patients significantly reduced their pain medication. For 6 of them, SCS was the sole treatment for their neuropathic pain.

Primary Author	Study Type	Diagnosis	# of Subjects at Baseline / at Last Follow-up	Outcomes
Pluijms (2012)	Prospective, non-comparative	Painful Diabetic Polyneuropathy (PDP) in the lower limbs	Baseline:15 12 mo:11	**Pain Relief** Statistically significant reduction of Day (60%, $p < 0.001$), Night (47%, $p < 0.01$ and Peak (22%, $p < 0.01$) pain scores in patients who received treatment. Of the Intent to Treat patients, 47% (7/15) had ≥ 50% Day pain relief, and 20% (3/15) had ≥ 50%Night and Peak pain relief. **Quality Of Life** When compared with the baseline, EQ-5D utility scores significantly increased at 2 weeks and 3 months; SF-36 PCS significantly increased at 3 and 12 months; SF-36 MCS did not increase significantly.
Slangen (2013)			Baseline:15 36 mo:11	**Pain Relief** At 36 months, 64% (7/11) patients who received treatment had ≥ 50% pain relief. **Quality Of Life** Improvement in quality of life was seen in 64% patients at 12 months; 55% at 24 months, and 64% at 36 months.
de Vos (2014a)	Prospective single-center	Painful Diabetic Neuropathy and FBSS	Baseline:12 Last FU:12 Tonic 1.8yr Burst 2 wk	**Pain Relief** Statistically significant pain relief obtained with both Tonic and Burst SCS treatments: Tonic: 58%, $p < 0.001$ Burst: 77%, $p < 0.001$
de Vos (2014b)* Duarte (2016)	Prospective, RCT, parallel design with 2:1 allocation comparing 'SCS + CMP' vs. 'CMP' to treat PDN	Painful Diabetic Neuropathy (PDN) in the lower extremities	Baseline: SCS: 40 Control: 20 6 mo: SCS: 36 Control: 18	**Pain Relief** SCS patients had 58% pain relief at last follow up ($p < 0.001$) while Control patients did not have statistically significant pain relief ($p = 0.97$). 63% (25/40) of SCS patients had ≥ 50% pain relief compared to 5% (1/20) Control patients. **Quality Of Life** At 6 months, SCS group reported larger improvement in quality of life as compared to the Control group. **Medication use** After 6 months, the SCS group had a statistically significant improvement in MQS III score ($p < 0.001$), which indicates a significant reduction in analgesic intake.

Primary Author	Study Type	Diagnosis	# of Subjects at Baseline / at Last Follow-up	Outcomes
Slangen (2014) van Beek (2015)	Prospective, multi-center RCT, parallel design with 3:2 allocation comparing 'SCS + best medical treatment' vs. 'best medical treatment' to treat PDPN	Painful Diabetic Peripheral Neuropathy (PDPN) in the lower limbs	ITT Baseline: SCS: 22 Control 14 6 mo: SCS: 19 Control: 14 RT Baseline 17 3 mo: 16 6 mo: 16 9 mo: 16 12 mo: 16 24 mo: 15	**Pain Relief** Pain reduction at 6 mo SCS vs. Control (Intent To Treat) Day: SCS 44%, Control 0% ($p < 0.001$) Night: SCS 38%, Control 12% ($p < 0.003$) For patients who received SCS At 3 months: Patients had 59% Day and 57% Night pain relief. 94% (15/17) patients had SCS treatment success. At 24 months: Patients had 45% Day and 48% Night pain relief. 65% (11/17) patients had SCS treatment success**. **Quality Of Life** ITT: No significant difference between SCS and Control groups at 6 months. RT: Compared to baseline, SCS treatment significantly increased EQ-5D utility scores at 3, 6, 9 and 12 months, but not at 24 months. **Disability** ITT: Both PSI and PII scores significantly improved in SCS group compared with the Control group. RT: Compared with baseline, SCS treatment significantly improved both PSI and PII scores of mBPI-DPN at 3, 6, 9 and 12 months. At 24 months, only PII score is significantly different. **Medication use (ITT)** SCS group: 7 out of 22 patients (32%) were able to reduce their pain medication, and for 2 of them, the SCS became the sole treatment for their PDPN pain. 12 patients (55%) did not change their medication in combination with SCS treatment. Control group: 4 of 14 patients (29%) reported an increased use of medication compared with baseline, and 1 patient changed to another category of neuropathic pain medication. In 9 (64%) patients, medication use was unchanged as compared with baseline.

Primary Author	Study Type	Diagnosis	# of Subjects at Baseline / at Last Follow-up	Outcomes
Van Beek (2018) – *combined cohort from Pluijms (2012) and Slangen (2014)*	Multi-center cohort study of SCS to treat PDPN with analyses of predictors of success. Patients pooled from Pluijms 2012 and Slangen 2014.	Painful Diabetic Peripheral Neuropathy (PDPN) in the lower limbs	Baseline 48 12 mo: 36 24 mo: 35 36 mo: 34 48 mo: 30 60 mo: 22	**Pain Relief** At 24 months: Patients had 39% Day and Night pain relief. 71% (25/35) patients had SCS treatment success. At last follow-up of 60 months: Patients had 36% Day and 31% Night pain relief. 55% (12/22) patients had SCS treatment success**. **Medication use** 9 patients reported an increased use of pain medication at their last assessment compared with baseline, whereas 10 reported less pain medication and 21 did not change their pain medication.

* The results reported in de Vos (2014b) were derived from the intention-to-treat analysis.

SCS treatment success in Slangen (2014) and van Beek (2015, 2018) was defined as: ≥ 50% relief of pain intensity on an NRS for 4 days during daytime or nighttime or a score of ≥ 6 on a 7-point Likert scale (1 = very much worse and 7 = very much improved) of the PGIC scale for pain and sleep.

Abbreviation: NR= not reported; RT= received treatment; ITT= intent-to-treat; CMP = conventional medical practice; RCT = randomized control trial; FBSS = Failed back surgery syndrome; QoL = Quality of Life;

X.2 RELIEF Study

A. Study Design

RELIEF was a global, multicenter, prospective, single-arm study designed to collect real-world evidence for the use of Boston Scientific SCS Systems in the treatment of chronic pain within routine clinical practice. Enrolled participants were established patients in a medical practice who were eligible to receive neurostimulation therapy to treat their pain condition utilizing a commercially-approved Boston Scientific SCS System per local labeling. Enrolled patients underwent a trial procedure using lead(s), per approved labeling and per standard of care. Patients with a successful trial continued participation in the study and received a permanent implant, as applicable. Following permanent implant, patients were followed up to 3 years. The study included several endpoints such as pain scores, quality of life and satisfaction with treatment.

A cohort of 43 patients who met the criteria of receiving SCS for the treatment of their chronic pain due to diabetic peripheral neuropathy (DPN) were identified from the study. The available data from this cohort of 43 patients was analyzed for safety evaluation. Follow-up data up to 36 months was included in the analysis.

B. Safety Results

8 device or procedure related Adverse Events were reported in the RELIEF Study among participants who met the criteria of receiving SCS for the treatment of their chronic pain due to DPN. A summary of events is provided in the table below. No unanticipated events were reported.

Table 9 : RELIEF Study - Device and procedure Adverse Events in DPN Cohort

Adverse Event	Number of Events	Serious AE
Hardware Related Adverse Events		
Device extrusion	1	No
Implant site pain	1	No
Procedure Related Adverse Events		
Headache	1	No
Hypoglycaemia	1	No
Implant site infection	1	Yes
Procedural pain	1	No
Pyrexia	1	No
Scar pain	1	No

A survival analysis (freedom from event) was conducted by comparing outcomes for a total of 43 DPN subjects to a total of 1438 non-DPN subjects, who were enrolled in the study and underwent IPG implantations. Infection, device site pain, wound problems, cerebrospinal fluid (CSF) leak, lead migration, and lead fracture events were compared

among DPN and non-DPN population. Although the point estimate of hazard ratio (HR) for infection and wound problem are greater than one, none of six event types showed statistical significance between DPN and non-DPN groups ($p > 0.05$).

D. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

This PMA is supported by clinical literature and no clinical study was performed by the applicant 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 Neurological Devices 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 11 publications from 6 prospective studies (several publications reported alternative analyses or long-term follow-up) described effectiveness outcomes associated with SCS to treat DPN. 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.

The two RCTs 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%. 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 DPN from one non-randomized

study and one RCT reflecting outcomes after 5 years of treatment showed a sustained pain relief at clinically meaningful levels.

The Boston Scientific SCS Systems are similar to the SCS systems reported in the published literature in intended use, device design, and output characteristics for paresthesia-based stimulation only. Therefore the effectiveness outcomes reported in the published literature support the effectiveness of SCS trherapy delivered by Boston Scientific SCS Systems for paresthesia-based stimulaton only in treatment of chronic pain due to DPN of the lower extremities.

In summary, the studies presented here show evidence of SCS effectiveness to treat DPN in the lower extremities. Across publications evaluating SCS for treatment of DPN, the data show clinically significant reductions in measured pain. They also show improved quality of life and disability and reductions in use of medications.

B. Safety Conclusions

The clinical evidence supporting the safety of Boston Scientific SCS Systems to treat DPN includes a systematic literature review of published scientific literature reporting SCS to treat chronic intractable pain in patients with diabetes in general. Safety data from 300 subjects treated with SCS for their DPN was included. An additional 2,235 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 DPN population were similar to that of the general SCS population. Published literature describing SCS to treat DPN 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.

The Boston Scientific SCS Systems are similar to the SCS systems reported in the published literature in intended use, device design, and output characteristics for paresthesia-based stimulation only. Therefore the safety profile of the Boston Scientific SCS Systems is expected to be the same as that reported in the published literature for use of SCS paresthesia-based stimulation in treatment of chronic pain in the lower extremities due to DPN. This conclusion is supplemented by an assessment of the data from the Boston Scientific RELIEF Study. There were no unanticipated adverse events in the DPN cohort from the Boston Scientific RELIEF Study.

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 DPN 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 71% 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 DPN that are sustained in the long-term.

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 notable differences. Diabetic patients treated with SCS had a higher 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 to treat DPN. 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 DPN. 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 DPN 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 DPN where the benefits outweigh the risks associated with the therapy.

1. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

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 indications for use. Beyond management of glycemic control, only palliative treatments are available to treat DPN. For intractable pain as a result of DPN, patients have few options after medical management. In two well-designed and executed randomized studies comparing SCS to treat DPN 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 chronic intractable pain from DPN of the lower extremities where the benefits outweigh the risks associated with the therapy.

XIII. CDRH DECISION

CDRH issued an approval order on 10/05/2023.

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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