SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: Prodigy, Proclaim, and Proclaim XR Spinal Cord Stimulation (SCS) Systems

Device Product Codes: LGW, QRB

Applicant's Name and Address: Abbott Medical, 6901 Preston Road
Plano, Texas 75024

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P010032/S189

Date of Notice of Approval to the Applicant: January 24, 2023

Abbott's implantable neurostimulation system was first approved for spinal cord stimulation as an aid in the management of chronic, intractable pain of the trunk and/or limbs including unilateral or bilateral pain associated with any of the following: failed back surgery syndrome, and intractable low back and leg pain on December 3, 2001 (PMA P010032). This supplement was submitted to expand the Indications for Use for the Abbott Spinal Cord Stimulation (SCS) Systems to include painful diabetic peripheral neuropathy (DPN) of the lower extremities.

The original PMA (P010032) was approved on December 3, 2001 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 any of the following: failed back surgery syndrome, and intractable low back and leg pain. The SSED to support this indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Prodigy, Proclaim, and Proclaim XR Spinal Cord Stimulation (SCS) Systems to include diabetic peripheral neuropathy of the extremities for the tonic stimulation mode.

I. INDICATIONS FOR USE

This spinal cord stimulation (SCS) systems 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 and leg pain, and diabetic peripheral neuropathy of the lower extremities.

II. CONTRAINDICATIONS

This system is contraindicated for patients who are unable to operate a system or who have failed to receive effective pain relief during trial stimulation.

III. WARNINGS AND PRECAUTIONS

Warnings and precautions are provided in the associated Abbott 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.

IV. DEVICE DESCRIPTION

System Description

The Abbott SCS System utilizes a multi-programmable neurostimulation system to deliver electrical stimulation to specific neural targets within the human body. The system consists of the following components:

- External Pulse Generator (EPG) – The EPG provides stimulation for patients during an evaluation or during intraoperative testing.
- Implantable Pulse Generator (IPG) - The IPG is implanted and delivers electrical stimulation via leads/extensions in the epidural space to provide SCS therapy. The IPG is implanted in a subcutaneous pocket and receives programming signals from an external Patient Programmer. The IPG decodes the signals and delivers stimulation pulses to the patient via a selected combination of output electrodes. The IPG is powered by a hermetically sealed battery enclosed within a hermetically sealed titanium case and uses an integrated circuit to generate electrical stimulation.
- Leads and Extensions - The lead delivers the stimulation to the targeted nerve through electrodes on the end of the lead. The extension connects the lead to the neurostimulator if necessary. The permanent and trial leads offer multiple lead configurations with variable lead body lengths and electrode spacing to satisfy placement preferences for the patient and implanting physician without compromising performance of the stimulator.
- Clinician Programmer (CP) - The CP interfaces with the IPG and is intended to be used by the clinician to noninvasively program and control device parameters.
- Patient Programmer - The Patient Programmer allows the patient to view, select, and control the programs that the clinician has prescribed.

- Patient recharger – Allows the patient to charge the battery of a rechargeable IPG. A plug-in charger recharges the patient recharger.

Principles of Operation

The Abbott SCS System is used as an aid in the management of chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome, intractable low back and leg pain, and diabetic peripheral neuropathy of the lower extremities. The surgical procedure involves implanting a lead into the epidural space along the spinal cord to deliver low-intensity electrical pulses to the nerve fibers. The lead is connected to an implantable pulse generator, which is the power source of the system. When turned on, the stimulator sends mild electrical pulses to the nerve fibers of the spinal cord via a selected combination of output electrodes on the connected lead; modifying and masking the pain signals, as shown in Figure 1. The stimulation settings are established noninvasively via an external Clinician Programmer to create customized therapy for patients. The stimulation programs created by clinicians can be selected by patients via a Patient Programmer to assist the patient in managing their prescribed stimulation programs.

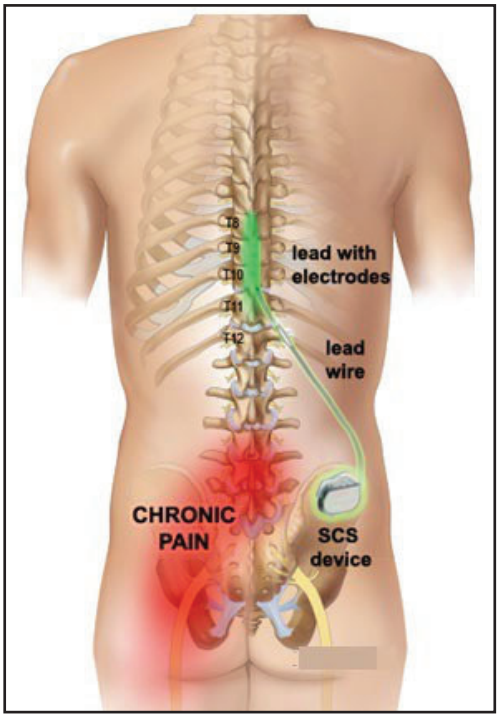

Figure 1. Representation of implanted SCS System

System Components

All of the Abbott 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 P010032. 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. Abbott SCS components

Device	Model #	Relevant PMA-S File #
Rechargeable Neurostimulation System		
Prodigy IPG Prodigy MRI IPG	3799 3772	P010032/S109
Prodigy Patient Programmer	3855 3856	P010032/S109
Prodigy Charging System	3730	P010032/S074
Primary Cell Neurostimulation System		
Proclaim XR 5 IPG Proclaim XR 7 IPG Proclaim 5 IPG Proclaim 7 IPG	3660 3662 3661 3663 3665 3667	P010032/S096
Clinician Programmer App	3874	P010032/S096
Patient Controller App	3875	P010032/S096
Trial Neurostimulation System		
Trial EPG	3599	P010032/S092
SCS Permanent Percutaneous Leads		
Octrode™ Leads	3183, 3186, 3189	P010032, P010032/S018
Quattrode™ Leads	3143, 3146, 3149, 3153, 3156, 3159	P010032, P010032/S018
SCS Permanent Paddle Leads		
Paddle Leads	3214, 3219, 3224, 3228, 3240, 3243, 3244, 3245, 3246, 3262, 3266, 3268, 3283, 3286, 3288	P010032, P010032/S010, P010032/S013, P010032/S018, P010032/S020, P010032/S026, P010032/S029
SCS Trial Percutaneous Leads		
Octrode™ Leads	3086	P010032
Quattrode™ Leads	3046	P010032

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

V. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices to the use of totally implanted IPG for spinal cord stimulation to treat chronic pain of trunk and limbs include:

1. Non-surgical treatment options for chronic pain patients include:
    a. Oral medication
    b. Rehabilitative therapy
    c. Transcutaneous electrical nerve stimulation (TENS);
    d. Behavior modification
    e. Neurolysis (i.e., Therapeutic nerve block, Cryoanalgesia RF Lesioning)

2. Surgical treatment options for chronic pain patients include:
    a. Sympathectomy- severing the nerve pathway
    b. Partially Implanted spinal cord stimulation (SCS) Systems – RF implantable spinal cord stimulators (the power source in this system is external).
    c. Commercially available fully implanted SCS Systems.

There are several alternatives for the treatment of diabetic peripheral neuropathy (DPN) of the lower extremities. Generally, two different approaches are used to treat these patients: glycemic control and symptomatic pain treatment. Treatment of the underlying diabetes, if possible, is generally the primary approach to pain management through improved control of blood-sugar levels. In addition, pharmacologic treatments are delivered to address pain symptoms. 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 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.

VI. MARKETING HISTORY

The Prodigy and Proclaim Spinal Cord Stimulation Systems for the treatment of chronic pain of trunk and limbs are currently approved for commercial distribution in Algeria, Argentina,

Aruba, Australia, Brazil, Canada, Colombia, Costa Rica, Ecuador, El Salvador, Estonia, Ethiopia, European Union, Hong Kong, India, Israel, Japan, Kuwait, Mexico, Monaco, New Zealand, Norway, Panama, Puerto Rico, Russian Fed., Saudi Arabia, Singapore, South Africa, South Korea, Switzerland, Taiwan, Turkey, United Kingdom, USA, United Arab Emirates. The Prodigy or Proclaim SCS systems have not been withdrawn from marketing for reasons related to safety and effectiveness of the device.

VII. 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 the device

- Undesirable changes in stimulation may occur over time. These changes in stimulation are possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, loose electrical connections and/or lead failure.
- Placement of a lead in the epidural space is a surgical procedure that may expose the patient to risks of epidural hemorrhage, hematoma, infection, spinal cord compression, and/or paralysis.
- Patients on anticoagulation therapies may be at greater risk for postoperative complications such as hematomas that can result in paralysis.
- Battery failure and/or battery leakage may occur.
- Radicular chest wall stimulation.
- Cerebrospinal Fluid leakage.
- Persistent pain at the electrode or IPG site.
- Seroma at the implant site.
- Lead migration, which can result in changes in stimulation and subsequent reduction in pain relief.
- Allergic or rejection response to implant materials.
- Infection
- Implant migration and/or local skin erosion.
- Paralysis, weakness, clumsiness, numbness or pain below the level of implantation.
- Loss of pain relief return patients to their original pain condition.
- Stimulation-dependent gastrointestinal symptoms such as nausea, diarrhea, incontinence, or constipation.
- Stimulation-dependent bladder symptoms such as urinary retention, incontinence, or frequency.

For the specific adverse events that occurred in the supporting data, please see Table 4 "Summary of Safety Results in Selected Studies" below.

VIII. SUMMARY OF NONCLINICAL STUDIES

Pre-clinical studies previously submitted to FDA in the Original PMA application (P010032) and supplements continue to support the safety of the commercially available Abbott 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 Abbott SCS therapy for the treatment of DPN of the lower extremities. The previously approved supplements which support the Abbott SCS therapy system and its components are listed above in Table 2.

IX. SUMMARY OF PRIMARY CLINICAL STUDIES

An Abbott 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 an Abbott implantable neurostimulation system has been previously established for the approved indications (see Section I, Table 1).

The clinical evidence supporting the safe and effective use of the Abbott implantable neurostimulation system in the diabetic neuropathy population is based on a systematic review of published clinical scientific literature of commercially available SCS systems (manufactured by Abbott and others). Primary evidence comes from two randomized controlled trials in patients with diabetic peripheral neuropathy (DPN). Additional supplemental clinical evidence for safety was identified through the analysis of Medicare claims data, investigating adverse event data related to the use of Abbott SCS systems in patients with diabetic neuropathy (DPN), and included reports reflecting the experience of patients treated with SCS for any condition where a diagnosis of diabetes was considered.

A. Study Design

The safety and effectiveness of the Abbott implantable neurostimulation system to treat DPN was based primarily on a systematic review of published scientific literature reporting on the use of 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 the Embase and PubMed databases for terms relating to SCS and diabetes. As a supplemental body of evidence to support safety, Abbott also analyzed relevant Medicare claims data from patients implanted with Abbott SCS systems. Finally, a systematic search of the published literature was conducted to identify recent guidelines on perioperative care of diabetic patients to inform the labeling.

Safety

The safety objective is to identify risks relevant to SCS to which diabetic patients are predisposed and to characterize the safety profile of SCS to treat DPN.

The safety profile of Abbott implantable SCS systems to treat DPN was characterized through analysis of published scientific literature and a Real-World Evidence (RWE) study of Medicare claims data from patients implanted with Abbott SCS systems. 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 DPN 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 the data from the Medicare claims database to create an overall safety profile.

Effectiveness

The effectiveness objective is to characterize the clinical benefits related to pain relief for SCS used to treat DPN when compared to the standard-of-care.

The effectiveness of Abbott implantable SCS systems to treat DPN was demonstrated through analysis of clinical study results identified from the systematic review of published scientific literature. Effectiveness was demonstrated by the probability of treatment success. The probability of treatment success (i.e., Responder Rate or proportion of successfully treated subjects) was defined by a specified percent reduction in pain rating 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. Medicare Claims Data

The Centers for Medicare and Medicaid Services (CMS) is a federal organization that administers both Medicare and Medicaid insurance programs. Medicare is for individuals over 65 years old, those under 65 with certain disabilities, and people with end stage renal disease (ESRD). CMS makes available Research Identifiable File Medicare Fee-for-service (FFS) claims data to innovators through the virtual research data center environment (VRDC). This longitudinal database includes all Medicare claims for 100% of Medicare FFS beneficiaries since the year 1999. In addition, Medicare claims are available for 100% of Medicare Advantage beneficiaries since the year 2015. For Medicare FFS data, quarterly data are available with a 4.5-month lag, and annual data are available with a 14-month lag. The Medicare Advantage data is available with approximately 24-month lag. Once eligible and enrolled in Medicare, beneficiaries tend to stay enrolled until death. This allows for long-term follow-up of device implants.

Data Selection

Patients implanted with an Abbott SCS system between January 1, 2014 and September 30, 2020 were identified in the Medicare databases and categorized into two cohorts based on Medicare claims diagnosis codes: 1) DPN: patients with a primary diagnosis of DPN or a

secondary diagnosis of DPN and a primary being chronic pain and 2) non-DPN: patients without any DPN diagnosis on the implant date or any evidence of a diagnosis in the year prior to implant. The incidence rate and cumulative incidence of common safety events up to 12 months following implantation were compared between the two cohorts to determine whether patients with DPN who are implanted with SCS exhibited an increased risk of common safety events when compared to the general population of SCS patients. For both cohorts, the incidence of safety events potentially associated with device-related surgeries (i.e., device removal, reimplant, or revision) following implantation were also evaluated. The safety events were identified from International Statistical Classification of Diseases and Related Health Problems (ICD) 9 and ICD 10 diagnosis codes that are used by Center for Medicare and Medicaid Services (CMS) for diagnostic, billing, and reporting purposes. A systematic review of the ICD-9 and ICD-10 codes was conducted to identify diagnostic codes that were associated with known SCS risks (e.g. infection and CSF leak), are specific to nervous system implants, or to neurostimulators for the spinal cord. These safety events include device events (e.g., lead migration, stimulator failure), negative device or procedure effects (e.g., infections, thrombosis, and hemorrhages that are specific to an implanted nervous system device), and general adverse events that are not specific to the device (e.g., CSF leak, infection due to any cause).

C. Literature Search Strategy

The databases searched include Embase and PubMed. The databases were searched to ensure comprehensive coverage of globally published clinical evidence for medical device products and therapies.

Abbott conducted two separate systematic searches and reviews. 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. Safety and effectiveness of SCS to treat DPN
    a. Search terms (including expanded terms): Diabetes AND spinal cord stimulation or dorsal column stimulation
    b. Search dates: 1984-2022
    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 studies on SCS to treat DPN 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.

2. 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: 2017-2022
   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.

Results of search and screening

C*linical practice guidelines for perioperative care of diabetic patients*

Initial screening was performed on 180 titles and abstracts resulting in the selection of 38 publications for full-text review. After full-text review, 31 publications were selected for inclusion. Guidelines are summarized in Table 3.

Table 3. Selected Guidelines

Author and Title	Summary	Recommendations	Noted complications
American Diabetes Association Professional Practice Committee. 16. Diabetes Care 2022[1] Diabetes care in the hospital: Standards of Medical Care in Diabetes—2022.	Article from the American Diabetes Association provides guidelines for the care of diabetic patients in the hospital. Article includes a specific section on the care of perioperative patients.	• The target range for blood glucose in the perioperative period should be 80–180 mg/dL (4.4–10.0 mmol/L). • A preoperative risk assessment should be performed for patients with diabetes who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure. • Metformin should be withheld on the day of surgery. • SGLT2 inhibitors must be discontinued 3–4 days before surgery. • Withhold any other oral glucose lowering agents the morning of surgery or procedure and give half of NPH dose or 75–80% doses of long acting analog or pump basal insulin. • Monitor blood glucose at least every 2–4 h while the patient is taking nothing by mouth and dose with short- or rapid- acting insulin as needed.	• "perioperative complications", no specifics provided.
Arthur et al. Braz J Cardiovasc Surg. 2018[2] Perioperative Management of the Diabetic Patient Referred to Cardiac Surgery	Presents recommendations for perioperative management of hyperglycemia in patients (with or without diabetes) undergoing cardiovascular surgery.	• All diabetic patients should receive continuous insulin infusion during surgery and for at least 24 hours postoperatively to maintain blood glucose levels < 180 mg/dL. • Intravenous insulin therapy is preferred due to rapid titration • Continuous insulin infusion should be used instead of subcutaneous injections or intermittent intravenous insulin bolus • Diabetic patients receiving continuous insulin should maintain it until after dinner in the night before surgery • All hypoglycemic agents and non-insulin oral diabetes medications should be maintained up to 24 hours before surgery • Level of glycated HbA1c should be assessed prior to surgery. adequate glycemic control is associated with HcA1c < 7% • Before surgery, blood glucose level should be below 180 mg/dL. • Patients with or without diabetes and persistently elevated blood glucose levels (> 180 mg/dL) should receive intravenous insulin infusions to maintain blood glucose levels ≤ 180 mg/dL during their stay in ICU	• Neurological events • Neurobehavioral deficits, and neurological-related deaths • All-cause mortality, myocardial infarction, acute heart failure • Recurring angina, wound infection

[1] American Diabetes Association Professional Practice. Diabetes care in the hospital: Standards of Medical Care in Diabetes—2022. Diabetes Care 1 January 2022; 45 (Supplement_1): S244–S253. https://doi.org/10.2337/dc22-S016

[2] Arthur et al. Perioperative Management of the Diabetic Patient Referred to Cardiac Surgery. Braz J Cardiovasc Surg. 2018 Nov-Dec;33(6):618-625. doi: 10.21470/1678-9741-2018-0147.

Author and Title	Summary	Recommendations	Noted complications
		• Patients requiring ≥ 3 days in ICU due to ventilator dependence or the need for inotropes, continuous venovenous hemodialysis or hemofiltration, and antiarrhythmic intra-aortic balloon or left ventricular assist device should receive continuous infusion of intravenous insulin to maintain a blood glucose level < 150 mg/dL, regardless of whether or not they are diabetics • Oral antidiabetics should be restarted in patients with adequate blood glucose levels, with few exceptions.	
Berhe et al. Intl. J. Surg. 2017[3] Guideline on perioperative glycemic control for patients 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
Bhattacharya et al. World J Diabetes. 2021[4] Expert opinion on the preoperative medical optimization of adults with diabetes undergoing metabolic surgery	Provides recommendations on perioperative medical management for individuals with diabetes mellitus who are undergoing metabolic surgery.	• Initial preoperative assessment should include a comprehensive medical, psychosocial and drug history, along with physical examination. • Tests for FPG (fasting plasma glucose), postprandial glucose and HbA1c should be included in laboratory workup. • A glycemic target of HbA1c <7% before surgery is a reasonable goal. • Medical nutrition therapy, physical exercise, and pharmacotherapy should be optimally integrated to attain that goal. Pharmacological agents known to induce weight loss, such as sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, should be considered as part of the	• Postoperative hyperglycemia • Wound Infection • Acute renal failure

[3] Berhe et al. Guideline on peri-operative glycemic control for adult patient with diabetic mellitus: Resource limited areas. Int J Surg Open 2017;9:1-6. doi: 10.1016/j.ijso.2017.07.001

[4] Bhattacharya et al. Expert opinion on the preoperative medical optimization of adults with diabetes undergoing metabolic surgery. World J Diabetes. 2021 Oct 15;12(10):1587-1621. doi: 10.4239/wjd.v12.i10.1587.

Author and Title	Summary	Recommendations	Noted complications
		treatment armamentarium whenever feasible. Drugs known to cause weight gain, such as sulfonylureas and thiazolidinediones, should be avoided as long-term therapeutic strategy if possible. The perioperative risks of deranged glycemic control vs benefits of early metabolic surgery have to be assessed on a case-to-case basis if glycemic control cannot be attained preoperatively despite optimal medical treatment. If a strategy of restricting calories with meal replacement therapy is employed in the preoperative weeks, the anti-diabetic medications would need to be reduced to prevent hypoglycemia • After admission, most non-insulin based therapies should be stopped, and the patient should be transitioned to insulin as per institutional practice. Severe degrees of hyperglycemia will require intravenous insulin infusion. Target glucose of 100 to 180 mg/dL (5.5-10 mmol/L) is acceptable in the perioperative period.	
Chan et al. Anaesth. Intensive Care Med. 2020[5] 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 electroccardiogram (ECG), 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
Cheisson et al. Anaesthesia, critical care & pain medicine. 2018[6] 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	• Infections • Delayed wound healing • Increased morbidity and mortality

[5] Chan et al. Preoperative cardiac optimization. Anaesthesia and Intensive Care Medicine. 2020; 21:10. doi:10.1016/j.mpaic.2020.07.008

[6] Cheisson et al. Perioperative management of adult diabetic patients. Intraoperative period. Anaesth Crit Care Pain Med. 2018; 37:S21-S25. doi: 10.1016/j.accpm.2018.02.018.

Author and Title	Summary	Recommendations	Noted complications
		• Manage risk of nausea and vomiting as to facilitate resumption of food intake after surgery • Manage post-operative pain closely to avoid hyperglycemia	
Cheisson et al. Anaesthesia Critical Care & Pain Medicine. 2018[7] 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
Cornelius et al. Anesth Prog. 2017[8] Patients With Type 2 Diabetes: Anesthetic Management in the Ambulatory Setting: Part 2: Pharmacology and Guidelines for Perioperative Management	An analysis of diabetic medication pharmacology and guidelines for blood glucose management in an ambulatory surgery setting.	• Antidiabetic drugs should not be taken on the day of surgery, but should not be discontinued the day prior to surgery. • Metformin may be discontinued 24-48 hours prior to surgery in patients with renal insufficiency. • Post-surgical medication regimens only should be restarted after normal food intake resumes. • Short-acting or rapid-acting insulin therapy should be withheld on morning of surgery • Long and intermediate acting insulin should be taken at 75-100% and 75% respectively the evening prior to the surgery day. Mixed/intermediate insulin doses should be taken in the morning at 50% of usual dose. • In the anesthetized diabetic patient, 70 mg/dL (3.9 mmol/L) of blood glucose is the trigger level for treatment for hypoglycemia. • Hypoglycemia is managed in conscious patients through diet + gel/glucose tablets. Unconscious patients can receive intravenous administration of dextrose. • Hyperglycemia is typically managed by subcutaneous or intravenous insulin administration. • Blood glucose level less than 180 mg/dL (10.0 mmol/L) is optimal for the ambulatory office setting.	• Postoperative nausea and vomiting • Compromised wound healing • Postoperative glycemic stability.

[7] Cheisson et al. Perioperative management of adult diabetic patients. Postoperative period. Anaesth Crit Care Pain Med. 2018; 37:S27-S30. doi: 10.1016/j.accpm.2018.02.023

[8] Cornelius et al. Patients With Type 2 Diabetes: Anesthetic Management in the Ambulatory Setting: Part 2: Pharmacology and Guidelines for Perioperative Management. Anesth Prog. 2017 Spring;64(1):39-44. doi: 10.2344/anpr-64-01-02.

Author and Title	Summary	Recommendations	Noted complications
		• Diabetic patients should be treated as the first patient early in the morning	

Dortch et al. Aesthetic Surgery Journal. 2016[9]
 	
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 post-anesthesia 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

Galtier et al. DIAMS study group. J Visc Surg. 2020[10] Bariatric surgery and the perioperative management of type 2 diabetes: Practical guidelines	Provides results of survey amongst physicians for guidelines of perioperative management for diabetes patients in the specific context of bariatric/metabolic surgery	• Pre-operatively, screening for retinopathy and cardiac ultrasound should be performed • HbA1c <8% is required in the pre-operative period for most experts screened. • 26.4% and 36.3% of experts determined that metformin should be stopped earlier than other hypoglycemic compounds for 48 and 24 hours before surgery respectively. • Oral hypoglycemic compounds should be stopped the morning of surgery, and GLP-1 agonists should be stopped 24 hours before the day of surgery (45%) or the day of (25%). • Fast-acting insulin and long-acting insulin are stopped in the morning of the surgery for respectively 60% and 45% of the experts. • Post-operatively, insulin pump treatment should not be stopped, basal insulin should be halved, and prandial insulin should be stopped except for severe hyperglycemia patients • Sulfonylureas should be stopped in immediate post-operative period	• Microvascular complications
Galway et al. World J Diabetes. 2021[11] Perioperative challenges in management of diabetic patients undergoing non-	Provides management guidelines for pre-operative assessment and management for non-cardiac surgery diabetes patients in the pre-	• In the preoperative phase, target Hba1c should be less than 8%. It is also recommended that the patient blood glucose not exceed 300 mL/dL, that they do not have a hyperosmolar hyperglycemic state, and do not have diabetic ketoacidosis. • Preoperatively, antidiabetic medication should be adjusted or withheld	• Postoperative complications: diabetic ketoacidosis, and hyperglycemic hyperosmolar

[9] Dortch et al. Perioperative glycemic control in plastic surgery: Review and discussion of an institutional protocol. Aesthetic Surgery J. 2016; 36(7):821-830. doi: 10.1093/asj/sjw064.
[10] Galtier et al. Bariatric surgery and the perioperative management of type 2 diabetes: Practical guidelines. J Vasc Surg. 2020 Feb;157(1):13-21. doi: 10.1016/j.jviscsurg.2019.07.012
[11] Galway et al. Perioperative challenges in management of diabetic patients undergoing non-cardiac surgery. World J Diabetes. 2021 Aug 15;12(8):1255-1266. doi: 10.4239/wjd.v12.i8.1255

Author and Title	Summary	Recommendations	Noted complications
cardiac surgery.	operative, intraoperative, and post-operative phases	accordingly to prevent accidental hyperglycemic/hypoglycemic episodes (should withhold metformin, glucagon-like peptide-1 agonists, sulfonylureas, and thiazolidinediones on day of surgery, and SGLT2 should be withheld at least 3 days before surgery) • Long-acting insulin should be reduced by 50% on the morning of surgery. Intermediate acting insulin should be maintained the day before surgery, but a 25% or 50% reduction in doses is recommended the night before and the day of surgery. Short acting insulin should generally be avoided on the day of surgery and only be administered according to actual blood glucose levels. • Intraoperatively, insulin should be administered when glucose levels are above 180 mg/dL, and intravenous glucose when the levels are below 70 mg/dL. The general range is from 110 - 180 mg/dL, with an upper limit of 216 mg/dL for patients with poor control.	nonketotic state • Acute renal failure, acute myocardial infarction • Longer ICU and hospital stays
Grant et al. Clinical Medicine, Journal of the Royal College of Physicians of London.[12] New guidance on the perioperative management of diabetes.	Practice guideline focusing on the perioperative management of diabetic patients from the UK's Center of Perioperative Care (CPOC)	Referrals for surgery on all patients with diabetes should be evaluated for: • HbA1c within 3 months of referral should be evaluated • Control of comorbidities and all medications Before Surgery - Assess and Optimize • Diabetes • Co-morbidities - Ensure shared decision making • Weight Management• Exercise • Smoking Cessation • If HbA1c <69 mmol/mol (8.5%) refer for optimization before undertaking surgery , where clinically safe and possible. Develop individualized plan for: • pre- and post-surgery medication changes • day surgery or inpatient surgery • Timing of surgery - scheduling of surgery should aim to minimize the period of fasting for patients with diabetes. • Communicate plan with patient, primary care, surgical, anesthetic and diabetes teams to ensure pre-operative optimization. On Admission: • ensure medicines reconciliation maintain capillary blood glucose at 6-12mmol/L document CBG, renal profile, lactate ketones in emergency patients ensure patients with T1DM are never denied insulin	• Surgical related infection • Raise plasma glucose levels • Increase insulin resistance • Diabetic ketoacidosis (DKA) • Hyperosmolar hyperglycaemic state (HHS) • Hyper- or hypoglycemia

[12] Grant et al. New guidance on the perioperative management of diabetes. Clinical Medicine, Journal of the Royal College of Physicians of London. 2022 Jan;22(1):41-44. doi: 10.7861/clinmed.2021-0355

Author and Title	Summary	Recommendations	Noted complications
		Medication Adjustment: • Long-acting or premixed insulin can usually be continued the day before and day of surgery but with a dose reduction (usually between 50%–80% depending on the type of insulin used). A rare but potentially serious and life-threatening association between SGLT-2i and euglycemic DKA has been recognized, the risk of which is increased when there is a restriction to food or fluid intake (such as fasting for surgical procedures). SLGT-2i should, therefore, be withheld in any patient who has been hospitalized for major surgery or acute serious illness. • Ketones levels should be monitored daily, even if asymptomatic with normal blood glucose levels, and the drugs should only be restarted once the clinical condition has stabilized and normal oral intake is established. During Surgery • Glucose should be maintained between 6-12mmol/L • capillary blood glucose (CBG) should be checked at induction and at least hourly if on insulin or insulin secretagogues, otherwise a minim of 2 hourly• immediate access to glucose meter, ketone meter and hypoglycemia management. Return to Ward • Blood glucose should continue to remain in the target range of 6–12 mmol/L • Aim for early eating and drinking should enable patients to promptly restore their usual diabetes regimen • Appropriate use of anti-emetics and analgesia, avoidance of intravenous fluids if able to meet needs orally or enterally, and promotion of mobilization. Discharge • Communicate with patients all medication changes, plan for future diabetes care, importance of self-management	
Harrop et al. Neurosurgery. 2021[13] Congress of Neurological Surgeons Systematic	This evidence-based guidelines provides a Grade B recommendation regarding HbA1c levels	• Diabetic individuals undergoing spine surgery should have a preoperative hemoglobin A1C (HbA1c) test before surgery and be counseled regarding the increased risk of reoperation or infection if the level is >7.5 mg/dL.	• Infection

[13] Harrop et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines for Perioperative Spine: Preoperative Surgical Risk Assessment. Neurosurgery. 2021 Oct 13;89(Suppl 1):S9-S18. doi: 10.1093/neuros/nyab316.

Author and Title	Summary	Recommendations	Noted complications
Review and Evidence-Based Guidelines for Perioperative Spine: Preoperative Surgical Risk Assessment	in diabetic patients undergoing spine surgery.		
Jinjing et al. Diabetes Metab Res Rev. 2021[14] Chinese clinical practice guidelines for perioperative blood glucose management	Article provides guidelines that are intended to improve perioperative blood glucose management.	• Perform comprehensive assessment of patients preoperative blood glucose levels and diabetes associated complications that can affect surgical prognosis. • Medical staff should communicate at least once during management of perioperative blood glucose. • Endocrinologist consult for patients with preoperative acute complications or severe chronic complications of diabetes. • Endocrinologist consult is recommended for perioperative patients with significant and frequent hypoglycemia, high glucose fluctuations and glucose levels that do not fall within the standard range. • For patients with Fasting plasma glucose (FPG) between 6.1 and 7 mmol/L and high risk of diabetes, oral glucose tolerance test (OGTT) is suggested for measuring the fasting glucose levels and venous blood glucose levels 2 h after oral administration of glucose. • For patients with high preoperative blood glucose levels but without confirmed diabetes, initial management according to the principles for patients with diabetes is suggested. • Persons with diabetes should have priority for surgery and preferred time for surgery is early in the morning. If surgery cannot be performed in the morning, monitor blood glucose levels continuously in the ward to detect and treat hypoglycemia and metabolic disorders due to fasting. • - if random blood glucose is ≥12.0 mmol/L or HbA1c is ≥9%, surgery delay is suggested, for elective surgeries. For patients in emergency surgery showing ketoacidosis or for patients in hyperosmolar coma, recommend that metabolic disorder, pH and osmotic pressure first be corrected. • Anesthesiologist should choose appropriate aesthetic and narcotic drugs according to type of surgery and patients' blood glucose level. During surgery, anesthesiologists should control depth of anesthesia, reduce stress	• Surgical site infection • Edema • Prerenal renal insufficiency

[14] Jinjing et al. Chinese clinical practice guidelines for perioperative blood glucose management. Chinese Society of Endocrinology of Chinese Medical Association. Diabetes Metab Res Rev. 2021 Oct;37(7):e3439. doi: 10.1002/dmrr.3439

Author and Title	Summary	Recommendations	Noted complications
		response, rationally use hormones and glucose-containing solutions, actively monitor blood glucose levels and promptly resolve issues that arise. • Target perioperative blood glucose level is 6.0-10.0 mmol/L for longer and medium-length surgeries. to prevent hypoglycemia, the target blood glucose level can be increased up to 12.0 mmol/L. Monitor everyc1-2 hr intraoperatively and every 2-4 h postoperatively. • For cardiac surgery patients, target is 8.3-11.1 mmol/L and for postoperative blood glucose control is less than 12.0 mmol/L. Monitor every 0.5-1 h intraoperatively and postoperatively every 204 h. • For neurosurgical patients, target glucose is 5.0-10.0 mmol/L for interoperative control and less than 12.0 mmol/L postoperatively. Monitor every 1-2 h intraoperatively and postoperatively every 2-4 hr. • For patients undergoing "fine surgery" (minimally invasive or microsurgical), the target preoperative blood glucose level is 5.0-7.2 mmol/L. for patients with a long disease course and who have difficulty for glucose control may be increased up to <8.3mmol/L. target for intraoperative blood glucose control is 6.7-11.1 mmol/L and postoperatively <12.0 mmol/L, Monitor intraoperatively every 1-2 h and postoperatively every 4-6 h. • For patients in postoperative intensive care or under mechanical ventilation and patients without cardiovascular disease or liver and kidney dysfunction, target glucose level is 7.8–10.0 mmol/L. For patients with cardiovascular and cerebrovascular disease or liver and kidney dysfunction, the target for blood glucose control is 8.0–12.0 mmol/L; however, the upper limit of the target blood glucose level can be extended up to 13.9 mmol/L. The blood glucose levels are monitored every 1–4 h (2C). • Strength staff awareness of the important of the prevention of hypoglycemia. • Patients should be managed to prevent hypoglycemia and keep blood glucose levels between 5.6 and 10.0 mmol/L. Glucose can be provided intravenously or orally depending on the patient conditions. • For surgeries less than 1 hour it is not necessary to perform insulin therapy for diabetic patients if blood glucose levels are adequately controlled by previously administered oral antidiabetic agents. During fasting period, sulfonylurea drugs and non sulfonylurea insulin secretagogues should be	

Author and Title	Summary	Recommendations	Noted complications
		stopped. SGLT2 inhibitors should be avoided in case of surgical procedures. • Patients under intraoperative insulin therapy should continue to receive insulin therapy during postoperative fasting period until they start eating, following which oral anti-diabetic agents can be resumed. • Diabetic patients with normal renal function do not need to stop taking metformin before surgery. If an intraoperative iodine contrast agent is necessary, metformin should not be taken 24h before surgery. For patients with abnormal renal function, metformin should not be taken 48 hours before surgery, and not restarted until renal function ins normal. • All staff administering insulin should be properly trained. • Use of insulin perioperatively is allowed an adjusted for the specific patient and level of blood glucose control achieved. • Diabetic patients receiving continuous enteral nutrition or intravenous nutritional support may use variable rate intravenous insulin infusions or continuous subcutaneous insulin infusions for blood glucose management. • Peripheral blood glucose levels should immediately be examined after surgery. • Patients receiving glucocorticoids postoperatively should undergo blood glucose monitoring every hour within 4 h of administration. diabetic patients receiving NSAIDs (particularly in combination with biguanides and glitazones) there is a possible risk of oedema and prerenal renal insufficiency caused by insufficient renal perfusion during hypovolemia. In such cases physicians should closely monitor blood glucose and renal function monitoring. • Establish team of nurses specializing in diabetes who are fully involved in management of perioperative blood glucose levels. • Hospitals should provide adequate support and education for patients and integrated into physician training.	
Kheniser et al. J Diabetes Complications. 2018[15] Diabetes management before, during, and after	Provides guidelines for pharmalogical regimens during the preoperative to postoperative period for diabetic patients	• A target HbA1c of < 6.5-7.0% is recommended prior to surgery, and 7.0-8.0% for patients with long-term diabetes or are poorly controlled. • Maintaining blood glucose levels between 140-180 mg/dL is recommended	• Hypoglycemic and hyperglycemic episodes • Diabetic ketoacidosis

[15] Kheniser et al. Diabetes management before, during, and after bariatric and metabolic surgery. J Diabetes Complications. 2018 Sep;32(9):870-875. doi: 10.1016/j.jdiacomp.2018.06.006

Author and Title	Summary	Recommendations	Noted complications
bariatric and metabolic surgery	undergoing metabolic/bariatric surgery.	• Adherence to a subcutaneous rapid acting or continuous insulin infusion is recommended when blood glucose levels are <180 mg/dL but > 140 mg/dL (subcutaneous) and above >180 mg/dL (continuous) • If patient has been using longer-acting insulins, half of basal dose can be administered in the morning of surgery • Premixed human insulin is not recommended, and another basal regimen at half the premixed dose during the morning of surgery as a replacement is recommended • Patient's insulin dosage should be below 0.6 units/kg to reduce risk of hypoglycemic events. • If blood glucose levels on admission are between 140-200 mg/dL, basal bolus regimen at 0.4/kg/day is given (evenly split between basal and bolus). For levels of 201-400 mg/dL, 0.5 units/kg/day are given. If fasting glucose is still >140 mg/dL, basal dose is increased by 20%. Basal insulin is decreased by 20% if hypoglycemic threshold is passed (<70 mg/dL) • Post-operative anti-diabetic regime should be adjusted depending on needs of the patient	(abdominal pain, nausea, vomiting)
Kuzulugil et al. Curr Opin Anaesthesiol. 2019[16] Recent advances in diabetes treatments and their perioperative implications	General perioperative management guideline for diabetes patients with an emphasis on glycemic control measures (avoiding hyperglycemia and hypoglycemia via therapeutic agents). There is also a short section on preoperative glycemic control.	• Optimal blood glucose target for hospitalized patients is approx. 106-180 mg/ml (6-10 mmol/L). • There is significant variability across clinical practices when it comes to anti-hyperglycemic medications • Metformin can be withheld on the day of surgery • Sulfonylureas should be ceased before surgery (~24 hour-period) • SGLT2 inhibitors should be ceased before surgery, and administered again postoperatively when patient is feeling well/eating normally • DPP4 inhibitors, and GLP-1 agonists can be withheld or continued perioperatively without major clinical outcome variance between the approaches • GLP-1 agonists possibly should be encouraged to be withheld due to some nausea effects • Improved hospital care delivery standards/clinical processes will help glycemic control.	• Increase in hospital stay • Diabetic ketoacidosis (SGLT2) • Nausea + Vomiting (GLP-1)

[16] Kuzulugil et al. Recent advances in diabetes treatments and their perioperative implications. Curr Opin Anaesthesiol. 2019 Jun;32(3):398-404. doi: 10.1097/ACO.0000000000000735

Author and Title	Summary	Recommendations	Noted complications
Leung et al. Health Serv Insights. 2017[17]	Perioperative guideline on assessment and management of diabetic patients and in regards surgery, anesthesia, hyperglycemic, medication regiment, transition to ward and discharge.	• Identification of non-diabetic patients who could possibly develop hyperglycemia due to surgery induced stress. Evaluation of HbA1c should be conducted to distinguish patients with elevated levels to identify unrecognized diabetes or prediabetes condition from "de novo" stress hyperglycemia. • Perioperative Glycemic Targets - Reference to ADA recommendation of targeting a perioperative glucose target of 80 to 180 mg/dL. • Preoperative Assessment - assessment of glycemic control and any diabetes associated complications •Comprehensive cardiac evaluation includes resting electrocardiography for intermediate and high-risk surgeries and if cardiac disease is suspected, stress or coronary artery angiography as indicated • Baseline laboratory date may include measurement of serum creatinine level to assess for chronic kidney disease, HbA1c if not previously available within the past 3 months, and blood glucose level, recommended for patients even without prior history of diabetes to avoid undiagnosed diabetes. • Patients treated with oral medications and/or noninsulin injectable - The morning of surgery, most organizations advise to discontinue oral and noninsulin injectable medications • SGLT-2 inhibitors may increase risk of volume depletion and DKA and should be withheld the day of surgery • Metformin should be avoided as it may increase the risk of renal insufficiency and lactic acidosis • Thiazolidinediones should be avoided due to potential fluid retention, peripheral edema and congestive heart failure. • Patients treated with insulin - Basal/bolus insulin regimens should be considered to be the most physiologic, as they best mimic normal pancreatic secretory function • Patients with type 1 diabetes or insulin-treated type 2 diabetes should be instructed to continue their usual meal plan and insulin regimen until the night before surgery. • Perioperative Glucose Monitoring and Insulin Strategies - Blood sugar should be checked before surgery and every 1 to 2 hrs. intraoperatively. Most diabetic patients can be managed with subcutaneous insulin perioperatively. Critically ill patients, insulin-treated patients undergoing longer and complicated surgeries or T1D patients should be managed with	• Hyperglycemia • Postoperative infection • Poor wound healing • Increased mortality • Metabolic derangements • Diabetic ketoacidosis (DKA)

[17] Leung et al. Perioperative Management of Patients with Diabetes. Health Serv Insights. 2017 Nov 15;10:1178632917735075. doi: 10.1177/1178632917735075

Author and Title	Summary	Recommendations	Noted complications
		an intravenous insulin infusion with frequent glucose monitoring (at least hourly) with adjustments to maintain glucose targets • Transition to Ward and Discharge - Patients should be transitioned to subcutaneous basal/bolus insulin regimen prior to intake of solid food. Insulin Infusion to subcutaneous insulin transitions should overlap at least 1 to 2 hrs. after first dose of subcutaneous insulin to prevent gap in insulin coverage. Patients previously not treated insulin, a subcutaneous regimen totaling 0.2 to 0.5 units/kg of body weight depending on the patient's insulin sensitivity.	
Livshetz & Nett. Tech. Orthop. 2019[18] 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
Mechanick et al. Endocr Pract. 2019[19] Clinical Practice Guidelines For The Perioperative Nutrition, Metabolic, And Nonsurgical Support Of Patients Undergoing Bariatric Procedures - 2019 Update: Cosponsored By American Association Of Clinical Endocrinologists/American College Of Endocrinology, The Obesity Society, American	Updated clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures.	• Preoperative glycemic control, A1C value of 6.5% to 7.0% or less and peri-procedural blood glucose levels of 80 to 180 mg/dL • Intra-/perioperative IV insulin is recommended for glycemic control. In type 2 diabetics, postoperatively, the use of all insulin secretagogues (sulfonylureas and meglitinides), sodium-glucose cotransporter-2 inhibitors and thiazolidinediones should be discontinued and insulin doses adjusted to minimize risk of hypoglycemia. Except for metformin and incretin-based therapies, antidiabetic medications should be withheld if there is no evidence of hyperglycemia. Metformin and or incretin-based therapies may be continued postoperatively in patients with type 2 diabetes until prolonged clinical resolution of type 2 diabetes is demonstrated by normalized glycemic targets. Subcutaneous insulin therapy, using a rapid-acting insulin analogue (insulin lispro, aspart, or glulisine) before meals and a basal long-acting insulin	

[18] Livshetz Perioperative Management of Diabetes for Total Joint Arthoplasty: A Consensus Article.Techniques in Orthopaedics. 34(3) (pp 167-171), 2019. doi: 10.1097/BTO.0000000000000398

[19] Mechanick et al. Clinical Practice Guidelines For The Perioperative Nutrition, Metabolic, And Nonsurgical Support Of Patients Undergoing Bariatric Procedures - 2019 Update: Cosponsored By American Association Of Clinical Endocrinologists/American College Of Endocrinology, The Obesity Society, American Society For Metabolic & Bariatric Surgery, Obesity Medicine Association, And American Society Of Anesthesiologists - Executive Summary. Endocr Pract. 2019 Dec;25(12):1346-1359. doi: 10.4158/GL-2019-0406

Author and Title	Summary	Recommendations	Noted complications
Society For Metabolic & Bariatric Surgery, Obesity Medicine Association, And American Society Of Anesthesiologists - Executive Summary		analogue (insulin glargine, detemir, or degludec) should be used to achieve glycemic targets (140 to 180 mg/dL) in hospitalized patients not in intensive care (Grade D). In the intensive care unit (ICU), IV regular insulin as part of a standard intensive insulin therapy protocol should be used to control hyperglycemia to a 140 to 180 mg/dL blood glucose target (Grade D). Endocrinology consultation should be considered for patients with type-1 diabetes (T1D), or with T2D and uncontrolled hyperglycemia (Grade D).	
Mumdzic & Munir, Surgery. 2020[20] 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
Robinson et al. Anaesth. Intensive Care Med. 2020[21] 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/mol (8.5%) 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)	• Post-operative infection (surgical site or systemic) • Cardiovascular events • Acute kidney injury • Stroke

[20] Mumdzic et al. Perioperative management of diabetes and corticosteriod supplementation. Surgery. 2020:38(12):819-826. doi: 10.1016/j.mpsur.2020.10.005.
[21] Robinson et al. Perioperative management of diabetes. Anaesth Intensive Care Med 2020; 21: 548-557 doi: 10.1016/j.mpaic.2020.08.001.

Author and Title	Summary	Recommendations	Noted complications
		• Patients should be provided with information on managing their diabetes upon discharge	
Roth et al. Interdisciplinary Diabetes and Nutrition in Operative Intensive Care Medicine Competence Group. Dtsch Arztebl Int. 2021[22] Blood Sugar Targets in Surgical Intensive Care—Management and Special Considerations in Patients With Diabetes	Provides blood sugar management guidelines for diabetic patients in intensive care units.	• A target range between 7.8 and 10 mmol/L (140-180 mg/dL) is the goal for diabetic patients in the intensive care unit, as it optimizes clinical outcomes while avoiding hypoglycemia. • Insulin therapy should not be initiated until a level of 10 mmol/L (180 mg/dL) • The range between 4.4 to 6.1 mmol/L (79-110 mg/dL) is not recommended for diabetes patients due to risk of hypoglycemia • Hyperglycemia and hypoglycemia should be avoided	• Wound/systemic infections • Immune dysfunction (impaired leukocyte function and phagocytosis) • Oxidative tissue stress, mitochondrial aberration, endothelial dysfunction • Hemodynamic effects (osmotic diuresis/dehydration, volume depletion, hypoperfusion, electrolyte/acid-base balance disorders
Simha & Shah. JAMA. 2019[23] 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

[22] Roth et al. Blood Sugar Targets in Surgical Intensive Care—Management and Special Considerations in Patients With Diabetes. Interdisciplinary Diabetes and Nutrition in Operative Intensive Care Medicine Competence Group. Dtsch Arztebl Int. 2021 Sep 24;118(38):629-636. doi: 10.3238/arztebl.m2021.0221

[23] Simha et al. Perioperative glucose control in patients with diabetes undergoing elective surgery. JAMA. 2019;321(4):399-400doi: 10.1001/jama.2018.20922

Author and Title	Summary	Recommendations	Noted complications
Song et al. Endocrine. 2019[24] Critical appraisal and systematic review of guidelines for perioperative diabetes management:	An analysis and comparison of various perioperative management guidelines, an assessment of quality through the AGREE II guideline evaluation tool.	• Blood glucose level target range is 5-12 mmol/L • HbA1c, hyperglycemia, and hypoglycemia should be managed. • Blood glucose should be monitored generally once per 1-2 hours for perioperative patients. • Oral anti-diabetic drugs (metformin, sulphonylureas, etc.) should be generally discontinued on day of surgery, but strategy and guidelines for this vary significantly. • Insulin therapy should be managed depending on the needs of the patient	
Stryker. The Journal of Arthroplasty. 2016[25] 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
Vervoort et al. J Card Surg. 2022[26] Sweet victory: Optimizing glycemic control after coronary artery bypass grafting	Presents guidelines on peri and post-operative glycemic control for patients specifically undergoing coronary artery bypass grafting.	• Glycemic control is best achieved with continuous insulin infusions rather than intermittent subcutaneous insulin injections or intermittent intravenous insulin boluses. • Patients with and without diabetes with high serum glucose (>180 mg/dl) should receive intravenous insulin infusions to maintain serum glucose <180 mg/dl for ICU care duration • Patients with diabetes should receive insulin infusion in OR and for at least 24h postoperatively to keep serum levels <180 mg/dl • Patients who need 3 or more days in ICU due to ventilatory dependency or general heart complications should receive continuous insulin infusion to keep blood glucose <150 mg/dl • Oral hypoglycemic medications should be restarted in patients who achieved target blood glucose levels if there aren't contraindications	• Sepsis

[24] Song et al. Critical appraisal and systematic review of guidelines for perioperative diabetes management: 2011-2017. Endocrine. 2019 Feb;63(2):204-212. doi: 10.1007/s12020-018-1786-y

[25] Stryker. Modifying Risk Factors: Strategies that work Diabetes Mellitus. The Journal of Arthroplasty. 2016; 31(8):1625-7. doi: 10.1016/j.arth.2016.02.084

[26] Vervoort et al. Sweet victory: Optimizing glycemic control after coronary artery bypass grafting. J Card Surg. 2022 Apr;37(4):937-940. doi: 10.1111/jocs.16278

Author and Title	Summary	Recommendations	Noted complications
		• If an intravenous insulin infusion is initiated in the preoperative period, it should be continued throughout the intraoperative and early postoperative period according to institutional protocols to maintain serum glucose ≤180 mg/dl. • A target blood glucose level ≤110 mg/dl should be achieved in the fasting and premeal states after transfer to the floor. • Before intravenous insulin infusions are discontinued, patients should be transitioned to a subcutaneous insulin schedule using institutional protocols. • Oral hypoglycemic medications should be restarted in patients who have achieved target blood glucose levels if there are no contraindications. Insulin dosages should be reduced accordingly. • Before discharge, all patients with diabetes and those who have started a new glycemic control regimen should receive inpatient education regarding glucose monitoring, medication administration (including subcutaneous insulin injection if necessary), nutrition, and lifestyle modification	
Vongsumran et al. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 13 (pp 2593-2601), 2020[27] Standardized glycemic management versus conventional glycemic management and postoperative outcomes in type 2 diabetes patients undergoing elective surgery.	A review of the efficacy of Conventional perioperative glycemic control protocol (CG) versus Standardized glycemic control protocol (SG). There was no significant difference in the percentage of hypoglycemic events between the CG and SG protocols	• Keeping blood glucose at less than 180 mg/dL but above 108 mg/dL can reduce mortality rates in critically ill surgical patients. Patients with blood glucose levels above 200 mg/dL perioperatively have an increased rate of infection. • Per FDA - SGLT-2i should be discontinued at least 3 days prior to scheduled surgery to reduce the risk of ketoacidosis.	• Mortality • Infection
Wang et al. Clinical Neurology and Neurosurgery, 2021[28] Perioperative optimization for patients undergoing elective spine surgery.	General perioperative guideline on management of patients in regard to medications, diabetes, hypertension, smoking, renal function, BMI,	• 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)	• Delayed wound healing • Infection • Thrombosis • Mortality

[27] Vongsumran et al. Standardized glycemic management versus conventional glycemic management and postoperative outcomes in type 2 diabetes patients undergoing elective surgery.Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 13 (pp 2593-2601), 2020. doi: 10.2147/DMSO.S262444

[28] Wang et al. Perioperative optimization for patients undergoing elective spine surgery. Clinical Neurology and Neurosurgery 2021; 202:106-445. doi: 10.1016/j.clineuro.2020.106445

Author and Title	Summary	Recommendations	Noted complications
	psychosocial aspects, and frailty.	• 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	

Safety and Effectiveness Literature Search

Initial screening was performed on 593 titles and abstracts resulting in the selection of 103 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: 22 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: 14 publications. Several studies resulted in multiple publications. Effectiveness data was extracted from all publications and included in total for each cohort. This information in reported in **Table 5**
- Meta-analyses: 6 publications reported meta-analyses of randomized controlled studies of SCS to treat DPN. The reports are summarized in **Table 6**.

Table 4. Summary of Safety Results in Selected Studies.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
Tesfaye et al. 1996[29], Daousi et al. 2005[30]	Prospective observational study for SCS use for the treatment of DPN. Included a double-blind test stimulation period.	10 patients, 8 received permanent implants	3.3-year mean, up to 7 years	3 patients died from myocardial infarction at 2 months, 2 years and 4 years post-implant. Lead migration requiring revision occurred in 2 patients, 2 patients required antibiotics for superficial wound infection, 1 system removed after 4 months for system failure, 1 hematoma at implant site without clinical impact, 1 lead failure due to trauma required replacement	Relevance: First study evaluating SCS for DPN specifically. Long term follow-up of safety/complications. Limitations: Small, single arm open label study. No comparator.
TenVaarwerk et al. 1999[31]	A retrospective, multicenter study of patients treated with spinal cord stimulation between 1987 and 1997	517 patients with angina pectoris and a permanent SCS implant, 14% identified as having Insulin Dependent Diabetes Mellitus	Median follow up was 23 months (range of 0 to 128 months)	Insulin dependent diabetes was the only important risk factor between the groups (Survivors vs non-survivors, $p = 0.05$). Diabetes ($p = 0.01$) was significantly correlated with mortality.	Relevance: Review of diabetes as a co-factor associated with mortality. Determination that there was a significant difference in mortality in the diabetic population. Limitations: Retrospective, follow uptimes variable, no separate DPN population. No analysis of diabetes related to SCS complications.
Petrakis et al. 1999[32]	Retrospective study of diabetic patients with peripheral arterial occlusive disease (PAOD) to evaluate pain relief and reduction of	64 diabetic PAOD patients	58 months mean follow up (20-128 months)	Of 14 patients with rest pain and no lesions (most similar to the DPN population being evaluated in this study), 1 patient required limb amputation, and one had a generator infection leading to removal of the device.	Relevance: Early study describing SCS in a diabetic population. PAOD is common in diabetic patients and frequently overlaps with DPN. Limitations: Open label, no comparator.

[29] Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet. 1996;348(9043):1698-1701.
[30] Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. Diabet Med. 2005;22(4):393-398.
[31] TenVaarwerk IA, Jessurun GA, DeJongste MJ, et al. Clinical outcome of patients treated with spinal cord stimulation for therapeutically refractory angina pectoris. The Working Group on Neurocardiology. Heart. 1999;82(1):82-88.
[32] Petrakis IE, Sciacca V. Epidural spinal cord electrical stimulation in diabetic critical lower limb ischemia. J Diabetes Complications. 1999;13(5-6):293-299.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
	amputation rate with SCS			Overall diabetic cohort had 8 battery replacement procedures following normal end of device life 2 lead migrations requiring lead revision 2 Infections requiring explant	
de Vos et al. 2009[33]	Prospective, open label, observational trial for diabetic patients with chronic pain	11 patients enrolled, 9 received permanent implant	30 months	Surgical revision due to inadequate connection between the lead and the extension cable in 2 patients. After revision the pain relief reappeared in both patients. One patient had a mild infection that was treated easily with antibiotics, without any influence on the SCS treatment. One death which was reported as unrelated to SCS.	Relevance: Few safety events which were resolvable. Limitations: Open label design. Single center, small trial without comparator.
Mekhail et al. 2011[34]	Retrospective review of case series in patients with SCS for intractable pain (Failed Back Surgery Syndrome, Complex Regional Pain Syndrome (CRPS), Peripheral Vascular Disease (PVD), visceral pain, neuropathy over a 5-year period	707 patients, 56 patients were diabetic	Variable, from 3 months to 7 years	Pain at the generator site (86), seroma without infection (1), lead migration (119), lead connection failure (50), and lead break (33). There were 32 (4.5%) patients that had infections. Of those with diabetes (56 patients total), 5 (9%) developed infections.	Relevance: Large evaluation of SCS experience over a 5-year period with a range of pain etiologies. This article reports safety issues primarily related to infection and device failures. Diabetic patients were noted to have a higher, though non-significant, rate of infection. Long-term follow up included. Limitations: No specific effectiveness data provided. Retrospective nature of study can lead to bias. Small diabetic population.

[33] de Vos CC, Rajan V, Steenbergen W, van der Aa HE, Buschman HP. Effect and safety of spinal cord stimulation for treatment of chronic pain caused by diabetic neuropathy. J Diabetes Complications. 2009;23(1):40-45.
[34] Mekhail NA, Mathews M, Nageeb F, Guirguis M, Mekhail MN, Cheng J. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. Pain Pract. 2011;11(2):148-153.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
Pluijms et al. 2012[35], Pluijms et al. 2015[36], Slangen et al. 2013[37], Slangen et al. 2014[38], van Beek et al. 2015[39], 2018[40]	Prospective, randomized, open-label multicenter RCT to assess the effectiveness of SCS in combination with best medical treatment (BMT) compared with BMT only in patients with DPN in the lower limbs. Patients were pooled from all subjects reported in Pluijms 2012 and Slangen 2014	49 patients enrolled 40 patients had a successful trial and received a permanent implant	5 years	- 13 battery replacements due to depletion (5 had 2 replacements) - 10 pain in the battery pocket (1 revision without complete resolution) - 9 reported uncomfortable stimulation - 6 device removals due to loss of efficacy -5 lead migrations with revisions - 4 lead failures which were replaced - 2 infections leading to explantation - 1 participant had a dural puncture during attempted trial lead implantation. 3 days later the patient had a subdural hematoma causing midline shift and eventual death	Relevance: Patients from a randomized, multi-center, 2 arm trial of SCS in patients with DPN compared to best medical treatment were combined with a cohort of patients in a single arm, open label study. Long term follow up to 5 years. Limitations: Open label. No control group for the 5 year follow up period. Study enrollment over 4 years, potential for increased expertise in surgeons or nurses who implant or change SCS settings.

[35] Pluijms WA, Slangen R, Bakkers M, et al. Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy: a pilot study. Br J Anaesth. 2012;109(4):623-629.
[36] Pluijms WA, Slangen R, van Kleef M, Joosten EA, Reulen JP. Increased contact heat evoked potential stimulation latencies in responders to spinal cord stimulation for painful diabetic polyneuropathy. Neuromodulation. 2015;18(2):126-132; discussion 132.
[37] Slangen R, Pluijms WA, Faber CG, Dirksen CD, Kessels AG, van Kleef M. Sustained effect of spinal cord stimulation on pain and quality of life in painful diabetic peripheral neuropathy. Br J Anaesth. 2013;111(6):1030-1031.
[38] Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care. 2014;37(11):3016-3024.
[39] van Beek M, Slangen R, Schaper NC, et al. Sustained Treatment Effect of Spinal Cord Stimulation in Painful Diabetic Peripheral Neuropathy: 24-Month Follow-up of a Prospective Two-Center Randomized Controlled Trial. Diabetes Care. 2015;38(9):e132-134.
[40] van Beek M, Geurts JW, Slangen R, et al. Severity of Neuropathy Is Associated With Long-term Spinal Cord Stimulation Outcome in Painful Diabetic Peripheral Neuropathy: Five-Year Follow-up of a Prospective Two-Center Clinical Trial. Diabetes Care. 2018;41(1):32-38.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
de Vos et al. Feb 2014[41]	Open label study in patients with 6 months experience SCS tonic stimulation to determine efficacy of switching to burst.	48 patients total, 12 with DPN	2 weeks	1 patient had worsening pain; side effects mentioned by patients were headaches (3), dizziness, and the sensation of "heavy legs" (2).	Relevance: First study assessing a switch to burst after having tonic stimulation. This is very different from patients who started with burst. Many missed the paresthesia as a feedback signal that the SCS system is functioning. Limitations: Only 2-week evaluation. No opportunity to change stimulation. Single center study with small number of DPN patients. Potential selection bias by reviewing patients with implants. Safety data not specific to DPN population.
de Vos et al. Nov 2014[42]	Open label, randomized trial with conventional medical practice (control) compared to SCS	60 patients with DPN were enrolled and randomized to SCS (n = 40) or control (n = 20) treatment. 3 SCS patients did not have successful trial stimulation, and 1 additional patient was withdrawn after deciding to enter another study. 36 completed 6-m f/u.	6 months	AEs related to the implantation included: pain due to the IPG (2), lead migration (1), perceived incomplete overlap of the paresthesia with the painful area during trial stimulation leading to a second electrode lead placed (1); infection during trial stimulation (1); coagulopathy in 1 patient complicated the implantation procedure and prolonged hospitalization. Potentially unrelated complications included 2 infections resulting in unstable blood glucose levels, 1 femur fracture, and 1 cardiac arrest. In the control group, there were 2 infections, 1 carotid artery stenosis, 1 myocardial infarction, 1 atrial fibrillation episode, and 1	Relevance: Randomized trial compared to BMT. Detailed adverse events information including relatedness. The authors indicate the need to carefully monitor blood glucose levels in the presence of infection. Limitations: Open label design with limited follow up (6 months) Patients were aware that they would be offered trial SCS after 6 months. It cannot be ruled out that some of the data collected in this group were biased by this prospect.

[41] de Vos CC, Bom MJ, Vanneste S, Lenders MW, de Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. Neuromodulation. 2014;17(2):152-159.
[42] de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain. 2014;155(11):2426-2431.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
				coronary bypass surgery.	
Bir et al. 2016[43]	Retrospective study, not specific to DPN. However, there is an analysis of the effect of diabetes on revision free survival.	141 cases where participants had an SCS system implanted	Mean follow up was 31.49 months	Revision free survival (RFS) in non-diabetics was 43 months, in diabetics was 35 months. The effect of diabetes on RFS was not statistically significant.	Relevance: Comparison of revision free survival curves with diabetes as a co-factor. Diabetes was not associated with a significant difference. Limitations: Retrospective (limitations on data collection, follow up times are variable), not specific to DPN.
Denisova et al. 2016[44]	Prospective, open label trial for patients with chronic spinal cord pain	Total of 136 patients with neuropathic pain syndrome underwent test stimulation, 75 received the permanent implant SCS.	6-18 months	2 SCS removals due to pain at generator implant site, 4 lead migrations required surgical revision/repositioning	Relevance: General SCS safety rates. Limitations: No data specific to the DPN population except for the statement that significant regression of pain was achieved in patients with diabetic neuropathy.
Hoelzer et al. 2017[45]	Multi-center, retrospective review in patients treated for FBSS, CRPS, Post-Herpetic Neuralgia, and other chronic pain conditions	2737 patients who had SCS implantation between Jan 2007 and June 2014 16% had diabetes	1 year	Primary placement infection rate: 2.19% Revision infection rate: 3.09% Total infection rate: 2.45% Rate of infection when no occlusive dressing was applied was 3.86% vs. 1.69% when an occlusive dressing was used. Rate of infection was 1.78% for patients who received post-operative antibiotics (78.3%). No post-operative antibiotics rate of infection was 4.09%.	Relevance: Large review that analyzed diabetes as a co-factor for prediction of surgical site infection. Diabetes did not demonstrate a statistically significant influence on rate of infection. Applying a sterile occlusive dressing while in the operating room significantly decreased the rate of infection generally. Limitations: Retrospective design, reporting bias, and the inherent restraint to identify causation. Authors found lack

[43] Bir SC, Konar S, Maiti T, Nanda A, Guthikonda B. Neuromodulation in intractable pain management: outcomes and predictors of revisions of spinal cord stimulators. Neurosurg Focus. 2016;40(5):E4.
[44] Denisova NP, Rogov DY, Rzaev DA, Khabarova EA, Dmitriev AB. Spinal cord stimulation in the treatment of chronic pain syndromes. Zh Vopr Neirokhir Im N N Burdenko. 2016;80(2):47-52.
[45] Hoelzer BC, Bendel MA, Deer TR, et al. Spinal Cord Stimulator Implant Infection Rates and Risk Factors: A Multicenter Retrospective Study. Neuromodulation. 2017;20(6):558-562.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
				Analysis of surgical site infection association with diabetes. Infection rate for patients with diabetes: 1.99% without diabetes: 2.54% (p = 0.49)	of continuity for some of the categorical variable data related to inconsistent reporting.
Falowski et al. 2019[46]	Retrospective analysis of patients with SCS implant from 2009-2014 included in a payer database to estimate rates of infection and other safety risk factors.	26,854 patients had a record of SCS generator implant or replacement during the study period. The final study population was 6615 patients after applying eligibility criteria. 5563 (84.1%) patients were identified as the initial group (patients with no evidence of prior SCS implant), and 1052 (15.9%) patients were identified as the replacement group (patients with evidence of prior SCS implant). Out of the 6615 patients that met the eligibility criteria, 1663 patients (25.1%) were either diagnosed with type 1 or type 2 diabetes.	12 months	3.11% of all SCS patients (206/6615) experienced an infection event within 12 months after their initial implantation date. The difference of infection rates between the initial group (3.09%; 172/5563) and the replacement group (3.23%, 34/1052) was not statistically significant (p = 0.8104). Of those that reported an infection in the initial group, 4.44% of them had type 1 diabetes while 3.41% of those without infection also had type 1 diabetes. Of those that reported an infection in the initial group, 25.60% of them had type 2 diabetes while 22.95% of those without infection also had type 2 diabetes. In total, out of the total 1663 diabetic patients, 59 of them (3.5%) reported an infection. There was no difference in the rate of diabetes between those that had infections and those that did not.	Relevance: A large retrospective study based on real-world data which provides valuable information on infection rates associated with SCS implants. There was no difference in the rate of diabetes between those that had infections and those that did not. Limitations: Uncertainty in the results stem from whether accurate occurrence of infection as well as the presence of comorbidities was adequately documented and coded. Also, there is a lack of detailed information about the infection including exact cause of the infection other than it being device related, and severity of infection.

[46] Falowski SM, Provenzano DA, Xia Y, Doth AH. Spinal Cord Stimulation Infection Rate and Risk Factors: Results From a United States Payer Database. Neuromodulation. 2019;22(2):179-189.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
Galan et al. 2020[47]	Patients with DPN were reported on separately from a larger prospective, single arm, multicenter, early feasibility study that evaluated SCS in patients with peripheral polyneuropathy.	9 patients with DPN of the lower limbs underwent a SCS trial stimulation, with 8 undergoing permanent implantation. 7 attended the 12 month follow up visit	12 months	Events considered procedure related: 1 incidence of implant site dehiscence 1 participant with pain in the leg 1 participant with implant site seroma Events considered non-procedure related: 1 hematuria 1 erectile dysfunction 1 hepatic failure 1 clostridium difficile infection 1 abdominal pain 1 intra-abdominal hemorrhage	Relevance: DPN patients reported on independently with detailed AE information. Limitations: Post-hoc analysis, limited samples size, therefore no statistical analyses performed. Adverse event rates difficult to assess due to small sample size.
Antonovich et al. 2021[48]	Single center, retrospective analysis of SCS reoperation rates for leads (paddle vs percutaneous).	291 patients 67% had a history of back surgery, 65 patients (22.34%) had diabetes	Up to 10 years	A diagnosis of diabetes was not associated with reoperation (univariate Hazard Ratio = 0.70; p = 0.197).	Relevance: Large data set that analyzed diabetes as a co-factor. No association between diabetes and lead/paddle type in time to re-operation. Limitations: Single center, retrospective study. No detailed AE data for diabetic population. Study reported a potential for charting errors, misinterpretation of charts, errors gathering data.
Petersen et al. 2021[49], Petersen et al. 2022[50]	Prospective, multi-center, open label, randomized trial 10kHz stimulation	216 patients were randomized at 1:1 ratio (103 control group and 113 in the treatment group)	6 - 12 months	18 study-related AEs in 14 subjects (12.4% of total study subjects in the treatment group): - 8 procedure-related infections (5.2%): three resolved with conservative	Relevance: Multi-site study, large RCT which includes a comprehensive list of all study related AEs. Detailed AE information was provided including determination of relation to device or

[47] Galan V, Scowcroft J, Chang P, et al. 10-kHz spinal cord stimulation treatment for painful diabetic neuropathy: results from post-hoc analysis of the SENZA-PPN study. Pain Manag. 2020;10(5):291-300.
[48] Antonovich DD, Gama W, Ritter A, et al. Reoperation Rates of Percutaneous and Paddle Leads in Spinal Cord Stimulator Systems: A Single-Center Retrospective Analysis. Pain Med. 2021;22(1):34-40.
[49] Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy: A Randomized Clinical Trial. JAMA Neurol. 2021;78(6):687-698.
[50] Petersen EA, Stauss TG, Scowcroft JA, et al. Durability of High-Frequency 10-kHz Spinal Cord Stimulation for Patients With Painful Diabetic Neuropathy Refractory to Conventional Treatments: 12-Month Results From a Randomized Controlled Trial. Diabetes Care. 2022;45(1):e3-e6.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
	was compared with conventional medical management 12 month follow up data included in secondary publication (Petersen et al., 2022)	104 patients had a trial stimulation, 90 subjects received a permanent implant 187 patients completed 6-month follow-up visits		treatments and patients continued in the study, five (3.2%) required device explant - 3 revisions; 2 for IPG site revision (1.3%), 1 for lead migration (0.6%); all three continued in the study - 2 wound dehiscence - 1 each of impaired healing, device extrusion, incision site pain, IPG site discomfort, lead migration, contact dermatitis, urticaria, radiculopathy, uncomfortable stimulation, gastroesophageal reflux, myalgia, arthralgia, and hyporeflexia and 2 SAE (i.e. explantation)	not. Limitations: It is unclear if the multiple adverse events occurred in the same patient and limited information is provided on the reasons for explantation.

Table 5. Summary of Effectiveness Results in Selected Studies.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
Tesfaye et al 1996[51]; Daousi et al 2005[52]	Prospective observational study for SCS use for the treatment of DPN. Included a double-blind test stimulation period.	10 patients received trial stimulation, 8 received permanent implant	14 months to 7.5 years	Trial success: 80% Statistically significant pain relief of both background and peak neuropathic pain (VAS Pain scores, McGill Pain Questionnaire) was achieved at 3 and 6 months and at the end of the initial study (6-20 months).	Relevance: First study evaluating SCS for DPN specifically. Long term follow-up. Limitations: Small sample size with only 4 patients completing 7.5 year follow up, single arm open label study. No comparator.

[51] Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet. 1996;348(9043):1698-1701.

[52] Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. Diabet Med. 2005;22(4):393-398.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
				Average 'peak' pain reductions: 3 months: 40.8% 6 months: 47.0% End of initial study: 56.2% 3.3 years: 57.5% 7.5 years: 36.2% Percent of patients able to achieve ≥50% reduction in 'peak' pain: 3 months: 42.9% (3 of 7) 6 months: 57.1% (4 of 7) End of initial study: 71.4% (5 of 7) 3.3 years: 66.7% (4 of 6 remaining) 7.5 years: none (all patients were experiencing pain relief, with a range of 30-45% reduction in pain).	
de Vos et al. Feb 2014[53]	Open label study in patients with 6 months experience SCS tonic stimulation to determine efficacy of switching to burst.	48 patients total, 12 with DPN.	2 weeks	Tonic stimulation caused 37% mean pain reduction. Burst stimulation caused an additional 25% reduction in pain (52% total). Pain reduction was best in patients with DPN (77%). 8 of 12 experienced additional pain reduction and preferred burst over tonic stimulation. Some patients indicated that they actually liked the paresthesia. The loss or change of the paresthesia and the inability to increase the stimulation amplitude and thereby the paresthesia intensity led some patients to prefer tonic stimulation over burst stimulation, in certain cases even despite of the larger pain reduction. In addition, some patients did not perceive the paresthesia as particularly comfortable but were able to shift their attention from the pain to the paresthesia and therefore appreciated it as a distraction from the pain.	Relevance: First assessment of switching to burst after having tonic stimulation. This is very different from patients who started with burst. Some missed the paresthesia as a feedback signal that the SCS system is functioning despite meaningful additional pain relief. A majority (8 of 12) of DPN patients preferred burst. Limitations: Only 2-week evaluation. No opportunity to change stimulation. Single center study with small number of DPN patients. Potential selection bias by reviewing patients with implants.

[53] de Vos CC, Bom MJ, Vanneste S, Lenders MW, de Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. Neuromodulation. 2014;17(2):152-159.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
				Success criteria was not established.	
de Vos et al. Nov 2014[54], Duarte et al. 2016[55]	Open label, randomized trial comparing conventional medical practice to SCS	60 patients with DPN were enrolled and randomized to SCS (n = 40) or control (n = 20) treatment. 3 SCS patients did not have successful trial stimulation, and 1 additional patient was withdrawn after deciding to enter into another study. 36 completed 6-month follow-up.	6 months	Trial stimulation success: 93% At 6 months 25 (63%) had 50% or greater reduction in pain (VAS) compared to control (5%); p<0.001. Moderate reductions (30–50 %) were reported by three patients (8%), minimum reductions in pain intensity (10–30 %) were reported by four patients (10%). 16 had more than 75% reduction (40%). There was also a significant reduction in analgesic intake in the SCS group. Average pain relief at 6 months: SCS 57.5%; control: 0% Patients also experienced significant improvements in Quality of Life as measured by the EQ-5D utility scores including mobility, usual activities, pain/discomfort and anxiety/depression (SCS: 0.39 improvement, control: 0.00 improvement).	Relevance: Randomized controlled trial. Data shows meaningful improvements in pain reduction, mobility, and anxiety/ depression. Randomized trial comparing to conventional medical practice. Limitations: Open label design. Patients were aware that they would be offered trial SCS after 6 months. It cannot be ruled out that some of the data collected in this group were biased by this prospect. Follow up limited to 6 months. Lack of individual patient data.
Slangen et al. 2014[56], van	Prospective, randomized, open-label, multicenter RCT to assess the effectiveness	36 randomized patients (22 for SCS and 14 for BMT) 17 of 22 had a positive trial period and went on to	2 years	Trial success rate: 77% Success defined as ≥50% relief of pain intensity on an NRS for 4 days or a score of ≥6 on a 7-point Likert scale (1 = very much worse, 6 = much	Relevance: RCT to compare SCS against BMT. Includes BMT patients who were able to crossover to the SCS arm. Multicenter. Data shows

[54] de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain. 2014;155(11):2426-2431.

[55] Duarte RV, Andronis L, Lenders MW, de Vos CC. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. Qual Life Res. 2016;25(7):1771-1777.

[56] Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care. 2014;37(11):3016-3024.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
Beek et al. 2015[57]	of SCS in combination with best medical treatment (BMT) compared with BMT alone in patients with DPN in the lower limbs.	permanent SCS implantation. 1 withdrew after infection and removal of the SCS implant.		improved and 7 = very much improved) of the PGIC scale for pain and sleep. At 6 months: -13 of 22 (59%) SCS patients achieved success, -1 out of 14 (7%) BMT patients achieved success -9 (41%) SCS patients and 0 in the control group had ≥50% reduction in pain on NRS, -12 (55%) SCS patients scored ≥6 (much improved) on the PGIC for pain and 8 (36%) scored ≥6 on the PGIC scale for sleep. No patients in the control group showed any difference in the PGIC scores. Mean pain score reduction on the NRS at 6 months was 3.1 for the SCS group (no change for BMT). Van Beek et al 2015 reported long term efficacy data out of the 17 successful trial stimulation patients. At 2 years, 8 (47%) and 6 (35%) patients reported a 50% pain reduction during day and night, respectively. Clinically significant improvements on the PGIC for pain and sleep were reported by nine (53%). Treatment success of SCS was observed in 11 out of 17 patients (64.7%). Average pain reduction at 12 months: 43.8% (day), 46.2% (night).	meaningful effects in pain reduction over a 2 year follow up. Limitations: Open label. No control group for the 2 year follow up period.
de Vos et al. 2009[58]	Prospective, open label, observational trial for diabetic patients with chronic pain.	11 patients enrolled, 9 received permanent implant	30 months	Trial stimulation success: 82% At 3 and 6 months: - 50% or greater pain relief was achieved in six patients (55%)	Relevance: Good long-term effectiveness seen in patients. Limitations: Open label design. Single center, small trial without comparator.

[57] van Beek M, Slangen R, Schaper NC, et al. Sustained Treatment Effect of Spinal Cord Stimulation in Painful Diabetic Peripheral Neuropathy: 24-Month Follow-up of a Prospective Two-Center Randomized Controlled Trial. Diabetes Care. 2015;38(9):e132-134.

[58] de Vos CC, Rajan V, Steenbergen W, van der Aa HE, Buschman HP. Effect and safety of spinal cord stimulation for treatment of chronic pain caused by diabetic neuropathy. J Diabetes Complications. 2009;23(1):40-45.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
				- 30–50% pain relief was seen in two patients (18%) - Average pain score was 77 at baseline and 34 at 6 months after implantation to yield an average pain reduction of 55.8%. After 12 months: - 50% or greater pain relief was achieved in seven patients (64%) - 30–50% pain relief was seen in one patient (9%) -Average pain score was 23 at 12 months to yield an average pain reduction of 70.1%. After 30 months: - 50% or greater pain relief was achieved in six patients (55%) - 30–50% pain relief was seen in one patient (9%) - Average pain score was still 23 at 30 months to yield an average pain reduction of 70.1%.	
Pluijms et al. 2012[59], Pluijms et al. 2015[60], Slangen et al. 2013[61]	Prospective, open-label, single center cohort study on the use of SCS in patient with DPN.	15 patients enrolled (ITT population), 11 patients received permanent implants after trial stimulation.	36 months	Trial success: 73% Clinically relevant pain reduction was defined as ≥50% decrease of pain intensity. Success of SCS treatment was defined as clinically relevant pain relief on 1 or more of: pain daytime, pain night, peak pain, or PGIC. Clinically relevant pain relief in 67% of patients (10 of 15) after 1 year of SCS treatment, 40% (6 of 15) at 24 months and 47% (7 of 15) at 36 months*.	Relevance: Long term follow up of DPN cohort that received SCS. Data shows meaningful effects in pain reduction over a long period of time. Limitations: Open label, single arm, single center study with a small number of patients.

[59] Pluijms WA, Slangen R, Bakkers M, et al. Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy: a pilot study. Br J Anaesth. 2012;109(4):623-629.
[60] Pluijms WA, Slangen R, van Kleef M, Joosten EA, Reulen JP. Increased contact heat evoked potential stimulation latencies in responders to spinal cord stimulation for painful diabetic polyneuropathy. Neuromodulation. 2015;18(2):126-132; discussion 132.
[61] Slangen R, Pluijms WA, Faber CG, Dirksen CD, Kessels AG, van Kleef M. Sustained effect of spinal cord stimulation on pain and quality of life in painful diabetic peripheral neuropathy. Br J Anaesth. 2013;111(6):1030-1031.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
				SCS treatment was also associated with improvement of sleep in 47% of patients (7 of 15) at 12 months. After 12 months of SCS treatment, daytime pain intensity was reduced by ≥50% in 7 patients (47%), nocturnal pain intensity was reduced by ≥50% in 3 patients (20%), and peak pain intensity was reduced by ≥50% in 3 patients (20%). Eight patients (53%) reported painful symptoms to be "much improved" or "completely resolved." Treatment success was seen in 10 patients (67%) at 12 months. Improvement in QoL was seen in 47% of patients at 12 months, 40% at 24 months and 47% at 36 months. *Long term efficacy results reported by Slangen et al 2013 changed success calculations to compare against only those with a successful trial stimulation. For clarity, these numbers have been recalculated to match the 12-month values reported in the original publication.	
Petrakis et al. 1999[62]	Retrospective study of diabetic patients with peripheral-arterial occlusive disease (PAOD) to evaluate pain relief and reduction of amputation rate.	64 diabetic PAOD patients	20–128 month range: (58 months on average)	Of 14 patients with pain at rest, >75% pain relief or more was seen in 11 patients (79%). 1 additional patient had >50% pain relief.	Relevance: Early study describing SCS in a diabetic population. PAOD is common in diabetic patients and frequently overlaps with DPN. Shows meaningful improvement for pain relief. Limitations: Limited to patients with pharmacological failure and high pain levels. Open label, no comparator.

[62] Petrakis IE, Sciacca V. Epidural spinal cord electrical stimulation in diabetic critical lower limb ischemia. J Diabetes Complications. 1999;13(5-6):293-299.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
van Beek et al. 2018[63]	Multi-center cohort study of SCS to treat DPN with analyses of predictors of success. Combined cohorts from Puijms 2012[8] and Slangen 2014[11]	49 enrolled patients, 40 patients received a permanent implant.	5 years	Adjusted NRS pain score reductions of 50% or greater during the day or night was observed in: - 1 year: 42% (15 of 36) day, 36% (13 of 36) night - 2 years: 43% (15 of 35) day, 40% (14 of 35) night - 3 years: 47% (16 of 34) day, 35% (12 of 34) night - 4 years: 37% (11 of 30) day, 33% (10 of 30) night - 5 years: 36% (8 of 22) day, 32% (7 of 22) night The percentage of patients reporting (very) much improvement on the PGIC scale for pain and sleep were: - 1 year: 72% and 53% (26 and 19 of 36) - 2 years: 54% and 37% (19 and 13 of 35) - 3 years: 53% and 29% (18 and 10 of 34) - 4 years: 53% and 47% (16 and 14 of 30) - 5 years: 50% and 32% (11 and 7 of 22) Treatment success (SCS treatment success was defined as ≥50% pain relief on the basis of day and night NRS pain score for 4 days or a PGIC score for pain and sleep of ≥6 on a 7-point Likert scale (1 = very much worse, 7 = very much improved) was observed in: - 1 year: 86% (31 of 36) - 2 years: 71% (25 of 35) - 3 years: 77% (26 of 34) - 4 years: 67% (20 of 30) - 5 years: 55% (12 of 22) Average pain reduction at 12 months is 43.3% (day), 41.8% (night).	Relevance: 5 year follow up of two studies including one multi-center RCT. Also includes cross-over patients. High levels of treatment success in many patients out to 5 years. Limitations: No control groups for long-term data. Loss to follow up for some long-term time points may bias conclusions.

[63] van Beek M, Geurts JW, Slangen R, et al. Severity of Neuropathy Is Associated With Long-term Spinal Cord Stimulation Outcome in Painful Diabetic Peripheral Neuropathy: Five-Year Follow-up of a Prospective Two-Center Clinical Trial. Diabetes Care. 2018;41(1):32-38.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
Kumar et al. 1996[64]	Case series of patients with pain neuropathies.	30 patients presenting with various peripheral neuropathies (4 upper-limb, 17 thoracic, 9 lower-limb) treated with SCS. 4 patients had diabetic peripheral neuropathy. 19 patients underwent permanent implantation after responding positively to trial stimulation.	Average 87 month follow up (range of 36 – 149 months)	Of all 4 patients with DPN reported ≥50% pain relief at one year. After one year, one patient developed upper-limb pain that was not targeted with the SCS which may have led to a decrease in the perception of pain relief resulting in 1 failed treatment (≤50% pain relief) after one year.	Relevance: Very long term follow up showing long term efficacy. Early study that reported on DPN patients specifically. Limitations: Small case series in a range of peripheral neuropathies. Not randomized or blinded.

Table 6. Summary of Safety and Effectiveness Conclusions in Selected Meta-Analyses

Publication	Study Design	N	Safety Conclusions	Efficacy Conclusions
Hou et al. 2016[65]	Evaluation of literature to support the use of burst stimulation in the treatment of chronic pain	5 Manuscripts reviewed, 1 discussed DPN	No severe complications described. Only dizziness, headache or a sensation of heaviness or warmth in the legs.	At the time of this article was published, Burst SCS was a new approach. Based on the literature reviewed, the authors concluded that it has the potential to provide more pain reduction than tonic SCS without eliciting paresthesia.
Raghu et al. 2021[66]	Meta Analysis of neuromodulation for DPN. MEDLINE and Embase were searched for appropriate articles. Results were screened by 2 independent reviewers. RCT data	32 publications including 21 tonic SCS, 2 high frequency SCS, 2 burst SCS, 7 other stimulation modes	Risk of failing therapeutic trial was 16%, and risk of infection was 4%. Risk of lead problems requiring surgery to resolve were 13%: 4% per year of follow-up. IPG replacement was 0% at six months, 12% at two	In the two RCTs (n=59) SCS was shown to be superior to BMT at six months. Significant improvement in pain from baseline at 6-and 12-month post-operative follow-up in SCS case series by mITT and PPA, respectively. Long-term case follow-up

[64] Kumar K, Toth C, Nath RK. Spinal cord stimulation for chronic pain in peripheral neuropathy. Surg Neurol. 1996;46(4):363-369.
[65] Hou S, Kemp K, Grabois M. A Systematic Evaluation of Burst Spinal Cord Stimulation for Chronic Back and Limb Pain. Neuromodulation. 2016;19(4):398-405.
[66] Raghu ALB, Parker T, Aziz TZ, et al. Invasive Electrical Neuromodulation for the Treatment of Painful Diabetic Neuropathy: Systematic Review and Meta-Analysis. Neuromodulation. 2021;24(1):13-21.

Publication	Study Design	N	Safety Conclusions	Efficacy Conclusions
	was pooled and compared statistically using the inverse variance method and expressed as mean differences. The Cochrane risk of bias tool was used to assess bias.		years, 17% at three years, and 45% at five years. Following "permanent" implantation, likelihood of explantation was 20% by five years. One patient died from subdural hematoma.	demonstrates that clinical benefit appears to continue for many years. Mean difference in pain score reduction (0-100 scale) of 37.84 (95% CI 28.83 to 46.85; I2 = 0%). Pooled mean difference for EQ5D = 0.16 (CI 0.02 to 0.30; I2=0%) and EQ-VAS = 11.21 (CI 2.26 to 20.16)
Duarte et al. 2021[67]	Systematic Review of to identify RCTs that studied SCS in DPN. Search was carried out on Embase, MEDLINE and CENTRAL.	2 RCTs with 93 total patients and additional 2 long term follow up articles	Treatment-related adverse events were reported narratively, but no safety related calculations or conclusions were made.	The authors found a statistically significant reduction in pain intensity: pooled mean difference -3.13, (95% CI -4.19 to -2.08), I^2 = 0%) on SCS treatment compared with BMT. There was also a significant increase in patients that achieved at least a 50% reduction in pain intensity with SCS: pooled risk ratio 0.08, (95% CI 0.02-0.38), I^2 = 0%. Risk of Bias assessment using the revised Cochrane risk of bias tool (RoB 2.0). *The methods for the meta-analysis are transparent, reproducible, and follow best practice recommendations. The results of the meta-analysis are more comprehensive, considering multiple time points and the influence of missing data, and therefore provide more certainty on the effect of SCS in reduction of pain intensity and improvement in HRQoL.*

[67] Duarte RV, Nevitt S, Maden M, et al. Spinal cord stimulation for the management of painful diabetic neuropathy: a systematic review and meta-analysis of individual patient and aggregate data. Pain. 2021;162(11):2635-2643.

Publication	Study Design	N	Safety Conclusions	Efficacy Conclusions
Xu L, et al. 2022[68]	Review of all non-pharmacologic treatment options for DPN; PRISMA guided literature search.	15 articles on the use of SCS for pain management in in DPN reviewed in a qualitative analysis	Early studies reported higher infection rates after SCS in diabetic patients than the general population. But diabetes does not independently increase the rate of infection in patients receiving SCS. Root cause of increased infections not evaluated in most studies, so for the time being general guidelines to prevent surgical site infection should be strictly followed.	These studies evaluated provide moderate to strong evidence to support SCS to treat refractory DPN in the lower extremities (evidence level: 1B+). However, the use of SCS for upper extremity DPN remains to be investigated.
D'Souza et al. 2022[69]	PRISMA guided literature search and review of evidence to support neuromodulation for the treatment of DPN	21 Publications were selected including 15 for SCS	Providers need to be aware of common complications from SCS, which have yet to be elucidated in patients with DPN, such as risk for infection, meningitis, hematoma, lead migration, hardware malfunction. In the surgical setting, there is a potential association of hyperglycemia and infection risk in patients. More studies need to be conducted to elucidate this relationship.	Level I evidence supports SCS for the treatment of DPN. Level II-3 evidence is available to support switching from tonic to burst stimulation in patients as needed.
Pluijms et al. 2011[70]	Review of 4 SCS studies in DPN[2,3,6,32]	25 patients, 6 and 4 of whom had diabetes type-I and diabetes type-II respectively.	No serious SCS related complications, infections requiring antibiotics in 14%, surgical revision required in 24%	Patients achieving 50% pain relief (VAS) compared to baseline pain scores: 84% in early pain relief (trial simulation), 50% at 3 months, 52% at 6 months, 63% at 12 months, 63% in the 2.5 – 3-year range, and 57% at 7 years.

[68] Xu L, Sun Z, Casserly E, Nasr C, Cheng J, Xu J. Advances in Interventional Therapies for Painful Diabetic Neuropathy: A Systematic Review. Anesth Analg. 2022;134(6):1215-1228.
[69] D'Souza RS, Langford B, Dombovy-Johnson M, Abd-Elsayed A. Neuromodulation Interventions for the Treatment of Painful Diabetic Neuropathy: a Systematic Review. Curr Pain Headache Rep. 2022;26(5):365-377.
[70] Pluijms WA, Slangen R, Joosten EA, et al. Electrical spinal cord stimulation in painful diabetic polyneuropathy, a systematic review on treatment efficacy and safety. Eur J Pain. 2011;15(8):783-788.

Publication	Study Design	N	Safety Conclusions	Efficacy Conclusions
				Patients achieving stoppage of analgesic usage: 67% at 1 year, 47% in the 2,5-3-year range, and 29% at 7 years.

3. Safety and Effectiveness Results

a. 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. Twenty-two (22) of 28 records indicated that the glucose level in the perioperative stages should be below 180 mg/dL. HbA1c percentages were generally recommended to be below 8%, with several guidelines recommending postponement of elective surgeries if HbA1c levels ranging from 8% to 9%. The guidelines reviewed also provided recommendations regarding blood-sugar control medication. Metformin can generally be continued on the day of surgery but should be withheld at least 48 hours prior if patient has renal dysfunction. Sulfonylureas generally should be stopped on the day of and up to 24 hours before surgery. Insulin treatments during the perioperative phase were noted to vary significantly in methodology and are likely dependent on many factors unique to the patient's medical history and individual characteristics.

The clinical guidelines reviewed included reference to common complications for diabetic patients undergoing surgical procedures. These complications included wound infection, impaired/compromised wound healing, vascular complications/myocardial infarction, diabetic ketoacidosis (DKA), renal dysfunction and insufficiency, increased mortality and morbidity in postoperative window, immune system dysfunction, thrombosis, and hyper/hypoglycemia.

Additional analysis was performed to gain some perspective of the relative frequency of some of the risks above. From selected clinical guidelines, those articles describing the incremental risks were reviewed to evaluate the primary sources of the perioperative complications. The sources described rates of events in the diabetic population as well as the relative risk levels (described as Odds or Hazard Ratios). Sources were screened for similarity of populations studied as compared to SCS (elective, orthopedic or spinal surgery, etc.). The results of this analysis are in Table 7. Most noted perioperative events were more likely to occur in diabetic patients in patients with higher HbA1c levels, with odds ratios ranging from 1.17 to 6.07. Over the data sources reviewed, diabetic patients were twice as likely to have an infection and delayed wound healing may contribute to this risk, being 6 times more likely in patients with higher HbA1c levels (Han et al, 2013)[71]. Myocardial infarction was 1.5 times more likely to occur in uncontrolled diabetic patients based on a univariate analysis but did not reach significant levels in the multivariate analyses (Marchant et al. 2014)[72]. Stroke risk was also elevated in the same cohort (Marchant et al. 2014).

[71]Han HS, Kang SB. Relations between long-term glycemic control and postoperative wound and infectious complications after total knee arthroplasty in type 2 diabetics. Clin Orthop Surg. 2013;5(2):118-123.
[72]Marchant MH, Jr., Viens NA, Cook C, Vail TP, Bolognesi MP. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. J Bone Joint Surg Am. 2009;91(7):1621-1629.

Additional references provided information on the risk of CSF leaks and subdural hematomas in diabetic patients. Ha et al. 2016[73] 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.[74] Wang et al. 2014[75] reported increased incidence of subdural hematoma in diabetic patients (log-rand test, p<0.0001). Cox proportional hazard modeling resulted in an adjusted Hazard Ratio = 1.63.

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),[76] 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),[77] 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
	Browne et al. (2007),[78] Lumbar fusion surgery, Infection rate **0.68%**	Brown et al. (2007): OR = 1.52
	Anderson et al. (2017),[79] Spine surgery, Infection rate for highest risk groups undergoing laminectomy = **2.3%**	Anderson et al. (2017): OR = 2.04
	Marchant et al. (2009),[80] Total Joint Arthroplasty, Infection rate: **0.38%** in controlled diabetes and **1.18%** in uncontrolled diabetes	Marchant et al. (2009): OR = 2.28

[73] Ha B-J, Cheong JH, Yi H-J. Risk Factors for Cerebrospinal Fluid Leakage after Craniotomy and the Efficacy of Dural Sealants Application versus Dural Suturing Alone. Nerve. 2016;2(2):22-25.
[74] Ha B-J, Cheong JH, Yi H-J. Risk Factors for Cerebrospinal Fluid Leakage after Craniotomy and the Efficacy of Dural Sealants Application versus Dural Suturing Alone. Nerve. 2016;2(2):22-25.
[75] Wang IK, Chen HJ, Cheng YK, et al. Subdural hematoma in diabetic patients. Eur J Neurol. 2014;22(1):99-105
[76] Han HS, Kang SB. Relations between long-term glycemic control and postoperative wound and infectious complications after total knee arthroplasty in type 2 diabetics. Clin Orthop Surg. 2013;5(2):118-123.
[77] Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. Diabetes Care. 1999;22(9):1408-1414.
[78] Browne JA, Cook C, Pietrobon R, Bethel MA, Richardson WJ. Diabetes and early postoperative outcomes following lumbar fusion. Spine (Phila Pa 1976). 2007;32(20):2214-2219.
[79] Anderson PA, Savage JW, Vaccaro AR, et al. Prevention of Surgical Site Infection in Spine Surgery. Neurosurgery. 2017;80(3S):S114-S123.
[80] Marchant MH, Jr., Viens NA, Cook C, Vail TP, Bolognesi MP. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. J Bone Joint Surg Am. 2009;91(7):1621-1629.

	Wang et al. (2020),[81] Cardiac Surgery, Infection rate: 2.7%	Wang et al (2020): strong association between surgical site infection rate and higher preoperative HbA1c levels in diabetic patients after cardiac surgery OR=2.94
	Cancienne et al. (2017),[82] lumbar decompression, infection rate: 0.5%-3.5%	Cancienne et al. (2017): for diabetic patients with HbA1c levels ≥7.5%, OR = 2.9
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),[83] Cardiac Surgery, 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),[84] Craniotomy, Rates not specific to diabetic patients	Ha et al (2016): OR = 1.82 for CSF leak in diabetic patients.

Data on diabetic and specifically DPN patients treated with SCS is included in the following sections. The safety profile of SCS used in diabetic populations appears to be similar to 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.[85]

Real World Evidence Evaluation of Medicare Claims Data

Available data on 36,004 (DPN: 507 and non-DPN: 35,497) patients implanted with Abbott SCS systems were included in the safety analysis. Incidence rates and cumulative incidence at 12 months following implantation for a total of 23 safety events. The results indicate low incidences

[81] Wang J, Luo X, Jin X, et al. Effects of Preoperative HbA1c Levels on the Postoperative Outcomes of Coronary Artery Disease Surgical Treatment in Patients with Diabetes Mellitus and Nondiabetic Patients: A Systematic Review and Meta-Analysis. J Diabetes Res. 2020;2020:3547491.

[82]Cancienne JM, Werner BC, Chen DQ, Hassanzadeh H, Shimer AL. Perioperative hemoglobin A1c as a predictor of deep infection following single-level lumbar decompression in patients with diabetes. Spine J. 2017;17(8):1100-1105.

[83]Wang IK, Chen HJ, Cheng YK, et al. Subdural hematoma in diabetic patients. Eur J Neurol. 2015;22(1):99-105.

[84] Ha B-J, Cheong JH, Yi H-J. Risk Factors for Cerebrospinal Fluid Leakage after Craniotomy and the Efficacy of Dural Sealants Application versus Dural Suturing Alone. Nerve. 2016;2(2):22-25.

[85] ADA. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S211-S220. doi:10.2337/dc21-S015

of device or procedure related safety events in DPN patients implanted with SCS, including incidence rates of 2.6% for device specific infections, 2.2% for lead migration, 7.5% for lead failure, and 4.9% for stimulation issues that require adjustment of the stimulation settings. Furthermore, there was no statistically reliable evidence of a difference between DPN and non-DPN patients in the incidence and cumulative incidence for any safety events that were specific to the device/procedure. The incidence and cumulative incidence rates for safety events that are associated with device-related surgical procedures (i.e., revision, replacement, or removal) were also not significantly different between DPN and non-DPN patients. This suggests that the use of SCS in this patient population does not lead to increased risk of device related safety events or safety events that may be associated with a device-related surgeries following initial implantation.

Data on common device specific events analyzed in the Medicare claims data 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 DPN or by those reporting on patients with diabetes in general (DM).

Table 8. Common Adverse Events

			Adverse Event Counts (%)						
			Infection	Lead migration	Lead failure	Device site swelling or pain	Hematoma/ Erosion/ Wound Dehiscence	CSF Leak/ Dural tear	Uncomfortable stimulation / stimulation issues
	DPN SCS RWE study on Abbott devices[a]	n[i] = 507	13(2.6)[b]	11 (2.2)[c]	38 (7.5)[d]	<11 (0.2-2.0)[e]		<11 (0.2-2.0)	25 (4.0)[f]
DPN	Petersen (2021) Petersen (2022)	n[t,i] = 104	8 (7.7)	1 (1.0)		2 (1.9)	4 (3.8)		1 (1.0)
DPN	Pluijms (2012) Slangen (2013, 2014) van Beek (2015, 2018)	n[t,i] =49	2 (4.1)	5 (10.2)	4 (8.2)	10 (20.4)		1 (2)[h]	9 (18.4)
DPN	Galan (2020)	n[t,i] =9				1 (11.1)	1 (11.1)		
DPN	de Vos (2014)	n[t,i] =40	3 (7.5)[g]	1 (2.5)		2 (5)			2 (5)
DPN	de Vos (2009)	n[t,i] = 11	1 (9.1)		2 (18.2)				
DPN	Tesfaye (1996) Daousi (2005)	n[t,i] =10	2 (20)	2 (20)	1 (10)		1(10)		
DM	Falowski (2019)	n[t,i] =1663	59 (3.5)						
DM	Hoelzer (2017)	n[t,i] =452	9 (2.0)						
DM	Mekhail (2011)	n[t,i] = 56	5 (8.9)						
DM	Petrakis (1999)	n[t,i] = 64	2 (3.1)	2 (3.1)					
	Range		2.0%-20%	1.0%-20%	7.5%-18.2%	0.2%-20.4%	3.8%-11.1%	0.2%-2%	1.0%-18.4%

*Studies that did not include AE information specific to the diabetic or DPN population were not included in this table.

DPN: Diabetic peripheral neuropathy, DM: Diabetes mellitus

n[i]: Sample size reflects patients with DPN who were implanted with the permanent implantable pulse generator (IPG).

nt[i]: Sample sizes reflect subjects exposed to either the trial stimulation or permanent IPG implant as described in the individual publications.

a: Incidence rates at 12-month post-implant based on Abbott's Real World Evidence Study of Medicare claims based on Medicare ICD-9 and ICD-10 diagnosis codes.
b: Based on diagnosis codes that are specific to an implanted nervous system device, infection related to an implanted neurostimulator lead and infection related to an implanted neurostimulator IPG.
c: Based on diagnosis codes that are specific to displacement of implanted nervous system lead.
d: Based on diagnosis codes that are for mechanical breakdown of implanted nervous system lead and other mechanical complication of implanted nervous system lead.
e: Based on diagnosis codes that are for pain due to implanted nervous system device.
f: Based on diagnosis codes that are for encounters for adjustment and management of neurostimulator.
g: Two patients with infection also had fluctuations in their blood glucose levels.
h: CSF leak reported in one subject during aborted trial lead placement and reported in Slangen (2014).
i: Based on report of implant site seroma.

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 which may be of concern for diabetic patients when it comes to the delivery and management of SCS therapy.

- **Infection**

  Data on device or procedure related infections in DPN and diabetic patients indicate an infection rate ranging from 2.0-20%. The incidence of infection is comparable to overall rates of infection associated with SCS of 4.89% (range: 2.5 to 10%) as reported in a systematic literature review by Eldabe et al. (2016)[24]. Infections in the literature were either resolved using solely antibiotics or through removal of the infected components of the SCS followed by administration of antibiotics. Data from the RWE study suggest that in general patients diagnosed with DPN have higher risk of infection at 12 months following implantation and higher cumulative incidence of infection during the 12-month period following implantation than subjects who were not diagnosed with DPN. However, these infections are not necessarily device or procedure related. The results of the RWE study indicate that the incidence of device specific infections is 2.6%. The device specific infection rate falls with the 2-20% incidence range reported in the literature. Additionally, device-specific infections and infections that were associated with device-related surgical procedures (i.e., revision, replacement, or removal) were not significantly different between DPN and non-DPN patients (device-related infections: risk difference of 0.7%, 95% CI: -0.6 to 2.1%; infections associated with device related surgical procedures post implant: risk difference of 1.0%, 95% CI: -0.7 to 2.7%). This suggests that while DPN subjects have elevated all-cause infection rates, device specific infection and infections that are associated with a device-related post-implant surgeries are not significantly different between patients with DPN as compared to non-DPN patients implanted with SCS. This finding is consistent with the results of three large retrospective studies on SCS, which also reported no significant difference in the rate of device specific infection for patients with diabetes.[86,87,88] Therefore, the various sources of evidence are consistent and show DPN subjects in general do not have a higher risk of device/procedure related infections. The data also suggests that diabetic patients have an increased risk of all cause infection, however this risk can be appropriately communicated through device labeling and clinical guidelines.

  The only complications as a result of infections explicitly mentioned in the literature include device explantation, abscess formation, and changes in glucose level stability. Specifically, Peterson et al. (2022)[89] reported that out of eight patients who had procedure-

[86] Falowski SM, Provenzano DA, Xia Y, Doth AH. Spinal Cord Stimulation Infection Rate and Risk Factors: Results From a United States Payer Database. Neuromodulation. 2019;22(2):179-189.
[87] Hoelzer BC, Bendel MA, Deer TR, et al. Spinal Cord Stimulator Implant Infection Rates and Risk Factors: A Multicenter Retrospective Study. Neuromodulation. 2017;20(6):558-562.
[88] Mekhail NA, Mathews M, Nageeb F, Guirguis M, Mekhail MN, Cheng J. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. Pain Pract. 2011;11(2):148-153.
[89] Petersen EA, Stauss TG, Scowcroft JA, et al. Durability of High-Frequency 10-kHz Spinal Cord Stimulation for Patients With Painful Diabetic Neuropathy Refractory to Conventional Treatments: 12-Month Results From a Randomized Controlled Trial. Diabetes Care. 2022;45(1):e3-e6.

related infections, three were able to resolve the infection with conservative treatments with no specified complications, whereas five required surgical explantation of the device. Another infection related complication that is of note is an increased risk of blood glucose fluctuations. This risk is highlighted by de Vos et al. (2014)[90] in which two subjects experienced fluctuations in blood glucose levels in response to an infection. Although the study did not attribute these infections to the device, the impact of blood glucose fluctuations in diabetic patients that may arise from device-related infections can lead to increased morbidity and mortality in this patient population.

- **Hematoma/Erosion/Wound Dehiscence**

  Based on the literature, the incidence rate of hematoma/erosion/wound dehiscence ranged from 3.8%-20%. Diabetes is known to a be a potential risk factor for hematoma, erosion and wound dehiscence which can lead to infection. However, these rates may be underreported due to greater attention to infections that may result from this adverse event.

- **Cardiovascular events**

  Several reports of subject or patient death attributed to myocardial infarction (n=4) or heart failure (n=1) were included in the available data on SCS to treat DPN.[91,92] None were reported to be related to SCS procedures or therapy, though patients with poorly controlled diabetes may have an elevated risk for cardiovascular events in the perioperative period. In an analysis of outcomes in patients undergoing elective orthopedic surgery (Marchant et al, 2009)[93], 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; $p < 0.001$).

  It should be noted that although CSF Leak was evaluated in the RWE study, results of the study were not included in Table 1 above since the adverse events presented in the table are device or procedure related. The CSF leak safety event that was evaluated in Abbott's RWE study included all diagnosis codes that were related to CSF leak without regard to device or procedure causality. This approach was taken to induce a level of conservativeness in the incidence rate associated with this serious adverse event. Out of the 507 DPN patients, there were fewer than 11 patients that were identified with CSF leaks from the medical claims data. Due to confidentiality concerns and per CMS cell suppression policy[94], we are unable to report on patient data that have fewer than 11 subjects. As such CSF leak in the DPN patients may have occurred in one subject or in 10

[90] de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. *Pain.* 2014;155(11):2426-2431.
[91] Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. Diabet Med. 2005;22(4):393-398. doi:10.1111/j.1464-5491.2004.01410.x
[92] de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: A multicentre randomized clinical trial. Pain. 2014;155(11):2426-2431. doi:10.1016/j.pain.2014.08.031
[93] Marchant MH, Jr., Viens NA, Cook C, Vail TP, Bolognesi MP. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. J Bone Joint Surg Am. 2009;91(7):1621-1629.
[94] https://www.hhs.gov/guidance/document/cms-cell-suppression-policy

subjects, this range corresponds to an incidence rate ranging from 0.2 -2%. Additionally, there was no statistically reliable evidence of a difference in the incidence in CSF Leak between DPN and non-DPN subjects implanted with a SCS system (risk difference = 0.0 to 1.8%, 95% CI: -0.4,3.0%).

- **Dural puncture and CSF leak**

  Slangen et al. (2014) reported one death due to subdural hematoma after dural puncture during the trial. A review of the literature was conducted to identify publications that report of CSF leak in patients with diabetes. Specifically, data from craniotomy procedures in Ha et al. (2016)[95] and Hutter et al. (2014)[96] suggest that diabetes may be a risk factor for CSF leaks.

  However, the more invasive nature of craniotomy procedures limits the translation of this concern to SCS procedures. Wang et al. (2014)[97] also reported a 1.57-fold higher incidence of subdural hematoma in diabetic patients than in non-diabetic patients (2.04 vs. 1.30 per 1000 person-years), with an adjusted hazard ratio of 1.63 [95% confidence interval (CI) 1.43–1.85].

  Please note that although CSF Leak was evaluated in the RWE study, results of the study were not included in Table 8 above since the adverse events presented in the table are device or procedure related. The CSF leak safety event that was evaluated in Abbott's RWE study included all diagnosis codes that were related to CSF leak without regard to device or procedure causality. This approach was taken to induce a level of conservativeness in the incidence rate associated with this serious adverse event. Out of the 507 DPN patients, there were less than 11 patients that were identified with CSF leaks that were identified from the medical claims data. Due to confidentiality concerns and per CMS cell suppression policy[98], we are unable to report on patient data that have less than 11 subjects. As such CSF leak in the DPN patients may have occurred in one subject or in 10 subjects, this range corresponds to an incidence rate ranging from 0.2 -2%. Additionally, there was no statistically reliable evidence of a difference in the incidence in CSF Leak between DPN and non-DPN subjects implanted with a SCS system (risk difference = 0.0 to 1.8%, 95% CI: -0.4,3.0%).

[95] Ha B-J, Cheong JH, Yi H-J. Risk Factors for Cerebrospinal Fluid Leakage after Craniotomy and the Efficacy of Dural Sealants Application versus Dural Suturing Alone. Nerve. 2016;2(2):22-25.
[96] Hutter G, von Felten S, Sailer MH, Schulz M, Mariani L. Risk factors for postoperative CSF leakage after elective craniotomy and the efficacy of fleece-bound tissue sealing against dural suturing alone: a randomized controlled trial. J Neurosurg. 2014;121(3):735-744.
[97] Wang I-K, Chen H-J, Cheng Y-K, et al. Subdural hematoma in diabetic patients. Eur J Neurol. 2015;22(1):99-105. doi:10.1111/ene.12538
[98] https://www.hhs.gov/guidance/document/cms-cell-suppression-policy

- **Glycemic control**

  de Vos et al (2014)[99] reported 2 subjects experiencing fluctuations in blood glucose levels following infections. 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**

  TenVaarwerk et al. (1999)[100] published a multi-center retrospectives study characterizing the morbidity and mortality of patients treated with SCS for refractory Angina Pectoris. The study included 517 subjects treated with SCS between 1987 and 1997, 14% of which were identified as having insulin dependent Diabetes Mellitus (IDDM). A multi-variate analysis significantly correlated IDDM with mortality ($p = 0.01$). However, the health status of the population in this report limits the generalizability of this data to a broader population of DPN patients, especially to those patients without severe cardiovascular complications. Specifically, before spinal cord stimulation, 66% of the patients of the patients included in this study had experienced myocardial infarction, 68% of them had three vessel disease and in 24% the left ventricular ejection fraction (LVEF) was ≤40 %. Moreover, angioplasty and bypass surgery were performed in 17% and 58% of the subjects, respectively.

  Tesfaye et al. (1996) [101] and Daousi et al. (2005)[102] reported 3 deaths over the 7-year study period. These deaths occurred at 2 months, 2 years, and 4 years after implantation and were all attributed to myocardial infarction. All three subjects had reported continuous pain relief from regular use of their SCS until the time of their death.

  de Vos et al. (2009)[103] also reported one death out of the 11 patients who enrolled in the study. The authors noted that the causes of death was unrelated to SCS.

  de Vos et al. (2014) also reported one instance of prolonged hospitalization related to the implant procedure due to a coagulopathy. The publication also described one subject in the SCS group experienced a cardiac arrest unrelated to the study procedure.

  As discussed above, Slangen et al. (2014)[104] also reported one death out of 22 patients who were assigned to the SCS treatment group due to dural puncture which occurred during implantation of the trial stimulation lead. The dural puncture led to a subdural hematoma over the left hemisphere and a midline shift and the patient died 10 days after the surgery.

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[99] de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: A multicentre randomized clinical trial. Pain. 2014;155(11):2426-2431. doi:10.1016/j.pain.2014.08.031

[100] TenVaarwerk, I. A., et al. (1999). "Clinical outcome of patients treated with spinal cord stimulation for therapeutically refractory angina pectoris. The Working Group on Neurocardiology." Heart 82(1): 82-88.

[101] Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet. 1996;348(9043):1698-1701.

[102] Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. Diabet Med. 2005;22(4):393-398.

[103] de Vos CC, Rajan V, Steenbergen W, van der Aa HE, Buschman HP. Effect and safety of spinal cord stimulation for treatment of chronic pain caused by diabetic neuropathy. J Diabetes Complications. 2009;23(1):40-45.

[104] Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care. 2014;37(11):3016-3024

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.[105] 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). Antonovich et al. (2021) conducted a retrospective review of patients treated with SCS for chronic pain and found diabetes was not associated with reoperation (p = 0.197).[106]

- **Lead migration**
  Incidence rates for lead migration ranges from 1 – 20%. These rates are comparable to general lead migration rates found in other studies of SCS that were not specific to patients with DPN or diabetes. Specifically, Kim et al (2011)[107] reported radiographic evidence of lead migration of 13.63% and 12.67% for percutaneous and laminectomy style leads, respectively in patients implanted with SCS. As demonstrated by the RWE study, the risk of the lead migration was not significantly different from DPN and non-DPN patients.

- **Lead failure**
  The incidence of lead failure ranged from 7.5%-18.2%. Cases of lead failures could be divided into lead breakage or other mechanical complication or poor pain coverage (unrelated to lead migration). An analysis based on the RWE study comparing the lead failure rates between DPN and non-DPN patients implanted with a SCS showed no significant difference between the two groups.

[105] Bir SC, Konar S, Maiti T, Nanda A, Guthikonda B. Neuromodulation in intractable pain management: outcomes and predictors of revisions of spinal cord stimulators. Neurosurg Focus. 2016;40(5):E4.
[106] Antonovich DD, Gama W, Ritter A, et al. Reoperation Rates of Percutaneous and Paddle Leads in Spinal Cord Stimulator Systems: A Single-Center Retrospective Analysis. Pain Med. 2021;22(1):34-40.
[107] Kim DD, Vakharyia R, Kroll HR, Shuster A. Rates of lead migration and stimulation loss in spinal cord stimulation: a retrospective comparison of laminotomy versus percutaneous implantation. Pain Physician. 2011;14(6):513-524.

b. **Effectiveness Results**

Literature search results - Effectiveness

The evaluation of the effectiveness of the Abbott SCS System was conducted via a systematic review of published clinical studies that evaluated the effectiveness of legally marketed, fully implantable SCS systems in treating chronic, intractable pain in the trunk and/or limbs, and diabetic peripheral neuropathy of the lower extremities. The literature search identified 14 publications from 8 studies reporting efficacy results applicable to evaluate the efficacy of SCS for DPN (**Table 5**).

Non-comparative studies

Ten publications include data from 6 single-arm studies that evaluated the use of SCS to treat DPN.[108,109,110,111,112,113,114,115,116,117] SCS trial success rates ranged from 73% to 93%. The proportion of subjects assessed as successfully treated ranged from 55% to 100% with average pain relief ranging from 41% to 80% (up to 12 months). Successful treatment during long term follow up ranged from 40% to 77% (24 months to 7.5 years).

Comparative studies

Two randomized controlled trials (RCT) investigated the use of SCS to treat DPN; results from these studies were described in 5 publications.[118,119,120,121,122] Table 9 presents a comparison of the two initial studies which reported on the primary outcomes

[108] Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet. 1996;348(9043):1698-1701. doi:10.1016/S0140-6736(96)02467-1

[109] Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. Diabet Med. 2005;22(4):393-398. doi:10.1111/j.1464-5491.2004.01410.x

[110] de Vos CC, Rajan V, Steenbergen W, van der Aa HE, Buschman HPJ. Effect and safety of spinal cord stimulation for treatment of chronic pain caused by diabetic neuropathy. J Diabetes Complications. 2009;23(1):40-45. doi:10.1016/j.jdiacomp.2007.08.002

[111] de Vos, C. C., et al. (2014). "Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy." Neuromodulation 17(2): 152-159.

[112] Pluijms WA. Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy: A pilot study. Br J Anaesth. 2012;109(4):623-629. doi:10.1093/bja/aes251

[113] Slangen R, Pluijms WA, Faber CG, Dirksen CD, Kessels AGH, van Kleef M. Sustained effect of spinal cord stimulation on pain and quality of life in painful diabetic peripheral neuropathy. Br J Anaesth. 2013;111(6):1030-1031. doi: 10.1093/bja/aet397

[114] Pluijms, W. A., et al. (2015). "Increased contact heat evoked potential stimulation latencies in responders to spinal cord stimulation for painful diabetic polyneuropathy." Neuromodulation 18(2): 126-132; discussion 132.

[115] van Beek M, Geurts JW, Slangen R, et al. Severity of neuropathy is associated with long-term spinal cord stimulation outcome in painful diabetic peripheral neuropathy: Five-year follow-up of a prospective two-center

clinical trial. Diabetes Care. 2018;41(1):32-38. doi:10.2337/dc17-0983
[116] Petrakis IE, Sciacca V. Epidural spinal cord electrical stimulation in diabetic critical lower limb ischemia. Journal of Diabetes and its Complications JO - J Diabetes Complications. 1999;13(5-6):293-299.
[117] Kumar, K., et al. (1996). "Spinal cord stimulation for chronic pain in peripheral neuropathy." Surg Neurol 46(4): 363-369.
[118] de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: A multicentre randomized clinical trial. Pain. 2014;155(11):2426-2431. doi:10.1016/j.pain.2014.08.031
[119] Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: A prospective two-center randomized controlled trial. Diabetes Care. 2014;37(11):3016-3024. doi:10.2337/dc14-0684
[120] van Beek M, Slangen R, Schaper NC, et al. Sustained Treatment Effect of Spinal Cord Stimulation in Painful Diabetic Peripheral Neuropathy: 24-Month Follow-up of a Prospective Two-Center Randomized Controlled Trial. Diabetes Care. 2015;38(9):e132-4. doi:10.2337/dc15-0740
[121] Duarte RV, Andronis L, Lenders MWPM, de Vos CC. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. Qual Life Res. 2016;25(7):1771-1777. doi:10.1007/s11136-015-1211-4
[122] van Beek M, Geurts JW, Slangen R, et al. Severity of neuropathy is associated with long-term spinal cord stimulation outcome in painful diabetic peripheral neuropathy: Five-year follow-up of a prospective two-center clinical trial. Diabetes Care. 2018;41(1):32-38. doi:10.2337/dc17-0983

Table 9: Details of publications describing randomized studies on DPN

Publication	Slangen et al. 2014[123]	de Vos et al. 2014[124]
Sponsor	Maastricht University Medical Center (NCT01162993)	Medisch Spectrum Twente (ISRCTN03269533)
Population	Diabetes patients with moderate to severe DPN in the lower limbs who were refractory to conventional medical treatments for more than 12 months NPRS pain rating ≥ 5 18 and 80 years of age	Patients with DPN in the lower extremities for more than 1 year and refractory to conventional treatments 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 DPN), and gender. Fewer Type I diabetic subjects were included in Slangen et al.. However, 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.	de Vos et al.
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%

Primary pain-related outcome measures between the two trials were compared to determine if the trials demonstrated similar effectiveness levels within the two similar populations; the subject measure averages are shown in ***Table 12***. Pain-related outcomes were similar between studies with

[123] Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care. 2014;37(11):3016-3024.
[124] de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain. 2014;155(11):2426-2431.

slightly greater reductions in pain reported by de Vos et al. Control groups from both studies did not achieve any notable 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.		de Vos et al.	
	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] 95% CI not provided due to required distributional assumptions
[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

Because the two RCTs had highly similar trial designs and patient populations and both compared SCS to conventional medical management with primary endpoints at 6 months, 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. A random effects analysis of heterogeneity between studies supported homogenization (Cochran's Q = 0.113, p-value = 0.737; Higgin's I^2 test = 0.0%). The confidence intervals of these studies overlap and the estimate of odds ratios are consistent, demonstrating subjects treated with SCS for DPN are more likely to achieve ≥ 50% pain relief at 6 months. The overall mean logOR is 3.21 (95% CI 1.68 to 4.73) corresponding to an Odds Ratio of 24.8 in favor of treatment success with SCS treatment of DPN.

A second analysis based on fixed effects model on the risk differences was performed. Similar to the random effects analysis, there is not statistically reliable evidence of heterogeneity between the studies I^2= 0.0%, and Q = 0.129 (p= 0.719). The fixed effect model estimates a group difference of 55.3% with a 95% CI from 40.8% to 69.9% (see **Table 13**). The data pooled from both studies showed that the binomial responder rates (defined as ≥ 50% reduction in pain at 6-months) for all subjects randomized to receive SCS treatment was 62.9% and supports probability of treatment success.

Table 13: Fixed Effects Results for 50% Responder Rates

Measure	SCS (N= 62)	Control (N= 34)	Difference
Responder rate ≥ 50% reduction in pain as-treated	62.9% (49.7% - 74.8%) [1]	5.9% (0% - 19.7%) [2]	55.3% (40.8% - 69.8%) [3]
[1] Binomial interval calculated with x = 39 and n = 62. [2] Binomial interval calculated with x = 2 and n = 34. [3] Interval from Fixed Effect Meta Analysis shown above.			

Long-term effectiveness

Van Beek et al (2018)[125] published long-term follow-up results for subjects from the studies reported by Pluijms et al (2012)[126] and Slangen et al (2014)[127]. 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 a 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 (hazard ratio 3.9; p-value = 0.014). This suggests patients with severe neuropathy may be less likely to experience treatment success.

[125] van Beek M, Geurts JW, Slangen R, et al. Severity of Neuropathy Is Associated With Long-term Spinal Cord Stimulation Outcome in Painful Diabetic Peripheral Neuropathy: Five-Year Follow-up of a Prospective Two-Center Clinical Trial. Diabetes Care. 2018;41(1):32-38.

[126] Pluijms WA, Slangen R, Bakkers M, et al. Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy: a pilot study. Br J Anaesth. 2012;109(4):623-629.

[127] Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care. 2014;37(11):3016-3024.

4. **Pediatric Extrapolation**

We believe that existing clinical data can be leveraged to support a reasonable assurance of safety and effectiveness of the subject device in a 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. While FDA considers patients aged 18-21 to still be pediatric in nature, this is a population that requires no special considerations and is treated the same as an adult population 22 and older ("Transitional adolescent B"). The discussion below follows the decision tree in the FDA Guidance Document "Leveraging existing clinical data for extrapolation to pediatric uses of medical devices", issued June 21, 2016.

Diabetic peripheral neuropathy is a condition that can occur in individuals who are 18-21. Jaiswal et al (2017)[128] assessed the prevalence of DPN in pediatric populations with either type 1 or type 2 diabetes enrolled in a clinical study. Prevalence of DPN in pediatric patients with type 1 diabetes was found to be 7%, and 22% for pediatric patients with type 2 diabetes. This particular study enrolled 1,734 patients with type 1 compared to 258 with type 2 diabetes. The mean age of the type 1 diabetes patients was 18 ± 4 years, with a duration since diagnosis of 7.2 ± 1.2 years. Within the type 2 population, the mean age was 22 ± 3.5 years, with a duration since diagnosis of 7.9 ± 2 years.

To the best of our knowledge, there is no requirement that the prevalence meet or exceed a certain percentage in order to qualify for extrapolation.

There are endpoints present in the existing data sources that measure the device effects relevant to the intended pediatric population. The types of endpoints measured in adult populations are the same as those that would be used in pediatric subpopulations. These include the visual analog scale (VAS), numerical rating scale (NRS), among others. Clinical studies often consider adults to be 18 and older, and there are no special considerations for the 18-21 age range with respect to the assessment of safety or efficacy outcomes. Published articles such as one by Moser et al (2017)[129] evaluating the development of a "youth-report measure of DPN symptoms" focuses on patients under 17, which we are not including for consideration here.

The Abbott SCS system is implanted and there are no differences between the adult and pediatric populations in the location or duration of implantation that could affect safety or effectiveness in a clinically meaningful way.

The Abbott SCS system is a permanent implant, as noted previously. The positioning of the device is the same for adults 22 and older as would be for patients aged 18-21. There is no need for specific instructions related to the implantation of the device for the 18-21 age range relative to

[128] Jaiswal M, Divers J, Dabelea D,et al. Prevalence of and Risk Factors for Diabetic Peripheral Neuropathy in Youth With Type 1 and Type 2 Diabetes: SEARCH for Diabetes in Youth Study. Diabetes Care. 2017 Sep;40(9):1226-1232. doi: 10.2337/dc17-0179.

[129] Moser J, Lipman T, Langdon DR, Bevans KB. Development of a youth-report measure of DPN symptoms: Conceptualization and content validation. J Clin Transl Endocrinol. 2017 Jul 8;9:55-60. doi: 10.1016/j.jcte.2017.07.001.

the older than 22 population. Therefore, there are no differences in these attributes that could affect the safety or effectiveness of the device in a clinically meaningful way.

Additionally, there are no differences in device characteristics between pediatric and adult use that could affect safety or effectiveness in a clinically meaningful way. The Abbott SCS system needs no modifications to be used for a patient aged 18-21 compared to those patients 22 and older. Both adults aged 22 and older and patients aged 18-21 will use the same hardware, with the specific hardware selections being individualized according to the particular needs of the patient, as it is done currently. Similarly, the stimulation is set on an individual basis, and is not calibrated any differently for the 18-21 subpopulation. Therefore, there are no differences in device characteristics that could affect the safety or effectiveness of the device in a clinically meaningful way.

There are no unique characteristics of the device that could affect safety or effectiveness in a clinically meaningful way when used in the pediatric population. As mentioned above, the type of population to which we seek to extrapolate data includes transitional adolescents who are treated like adults. In that regard, there is no evidence to suggest that there are substantial differences between patients who are 18-21 with DPN and those who are 22 and older with DPN. Skeletal maturity is achieved by age 18, for example, and relative to a patient who is 22 any group differences are negligible. Therefore, there are no characteristics that are unique to the intended pediatric subpopulation that could affect the safety or effectiveness of the device in a clinically meaningful way.

There are no differences in the disease characteristics between pediatric and adult populations that could affect safety or effectiveness in a clinically meaningful way. While there may be differences in risk factors for the development of DPN, that is not important to the discussion either of extrapolation specifically or safety and effectiveness in general because the system is not intended for use in diagnosis of DPN – patients who will use the Abbott SCS system will have previously been diagnosed with DPN, the process of which is the same for adults 22 and older as it is for patients who may be aged 18-21.

With respect to the disease itself, we are not aware of any evidence to suggest an age-related difference in the clinical symptoms of DPN, such that the presentation of DPN symptoms in an 18-year old could be said to be different from those of a 22-year old in a clinically meaningful way.

As described above, we are not aware of any evidence to suggest there are age-related differences in the characteristics of the disease, nor are we aware of any unique characteristics between the intended 18-21 pediatric population and the adult population aged 22 and older. We are similarly not aware of any additional differences between the adult and pediatric populations that could affect the safety or effectiveness of the Abbott SCS system for the treatment of DPN in a clinically meaningful way.

Having established that the adult and intended pediatric subpopulations are sufficiently similar, the next question to be addressed is whether the adult data are of sufficient quality to permit extrapolation. It is our position that the data are in fact of sufficient quality to permit extrapolation.

The body of evidence described in this submission includes data from a significant number of study subjects and patients, and the studies that were analyzed have been peer-reviewed for publication. As will be described in the benefit-risk analysis section below, there is a reasonable amount of certainty present with respect to the evidence both for safety as well as effectiveness. If the evidence is sufficient to support a determination of a reasonable assurance of safety and effectiveness, it is also sufficient for the purposes of pediatric extrapolation. Therefore, we believe it is appropriate to extrapolate the adult data where SCS is used to treat DPN to the population aged 18-21.

5. Financial Disclosure

The assessment of effectiveness was supported by articles written de Vos et.al. and Slangen et al. These sources were either randomized controlled trials or prospective clinical studies, which in general, are considered to have minimal bias, and support the reliability of the data collected. It is for these reasons that we believe that none of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

X. 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.

XI. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

A total of 14 publications from 8 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 84 subjects. Two retrospective studies contained data on 68 patients with diabetic neuropathy, and 2 RCTs comparing SCS to the standard-of-care included a total of 96 subjects.

Two independent RCTs evaluating SCS to treat DPN 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.

The overall mean logOR is 3.21 (95% CI 1.68 to 4.73) corresponding to an Odds Ratio of 24.8 is in favor of treatment success with SCS treatment for DPN. The data pooled from both studies showed that the binomial responder rates (defined as ≥ 50% reduction in pain at 6-months) for all

subjects randomized to receive SCS treatment was 62.9% and supports probability of treatment success.

Long-term efficacy data on subjects treated with SCS to treat DPN from one nonrandomized study and one RCT reflecting outcomes after 5 years of treatment showed a sustained pain relief at clinically meaningful levels.

There were an additional 6 meta-analyses that independently reviewed effectiveness from previously published studies and determined that there was sufficiently strong evidence to support the use of SCS to treat DPN.

The data from these studies support the effectiveness of an Abbott implantable SCS system for treating patients who suffer from chronic, intractable pain of the trunk and/or limbs, including diabetic peripheral neuropathy of the lower extremities.

B. Safety Conclusions

The clinical evidence supporting the safety of Abbott implantable SCS systems to treat DPN includes a systematic literature review of published scientific articles reporting SCS to treat chronic intractable pain in patients with diabetes in general, and data from Medicare claims data on patients treated with SCS to treat DPN. Safety data from 730 subjects treated with SCS for their DPN was included. An additional 2235 patients were included across 4 studies which reported on diabetic patients treated with SCS. The rates of common adverse events in the DPN population were similar to that of the general SCS population. The literature highlighted some inherent risks that are associated with spinal cord stimulation in DPN subjects including, but not limited to, infection, delayed wound healing, cardiovascular events, dural puncture and subsequent subdural hematoma, and fluctuations in glycemic control. These events can be mitigated through appropriate patient selection, and/or by the use of appropriate surgical techniques and procedures and have been included in the labeling.

Published literature describing SCS to treat DPN and published clinical practice guidelines on perioperative care of diabetic patients provide information on specific inherent risks for the diabetic patient in the delivery and management of SCS therapy. These inherent risks include, but are not limited to, 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, and/or by the use of appropriate surgical techniques and procedures.

There were an additional 5 meta-analyses that independently reviewed safety information and determined that risks of SCS in the diabetic population were similar to conclusions from previously published studies.

Refer to the Information for Prescribers for safety information specifically addressing the diabetic population. Underlying health conditions related to diabetes or other diseases may disqualify some patients from receiving SCS.

C. Benefit-Risk Determination

Diabetic peripheral neuropathy is nerve damage caused by chronically high blood sugar and diabetes. It leads to numbness, loss of sensation, and sometimes pain in your feet, legs, or hands. It is the most common complication of diabetes.

About 60% to 70% of all people with diabetes will eventually develop peripheral neuropathy. Beyond management of glycemic control, only palliative treatments are available. The best way to prevent or manage DPN is to keep within the patient's target blood sugar range. If the patient has developed DPN, the primary treatment is pain relieving treatments. Currently, the anticonvulsant Lyrica (pregabalin)[130], the antidepressant Cymbalta (duloxetine)[131], and the opioid Nucynta (tapentadol)[132] are the only drugs approved by the FDA for the treatment of diabetic neuropathy.

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 primary benefit of the Abbott SCS system is the improvement in pain for diabetic peripheral neuropathy (DPN). The patients have exhausted most other options and are mostly on a regimen of pharmacologic treatments that may include opioids, anticonvulsants, and antidepressants. Often times these options no longer are effective and the patient needs other solutions to treat their DPN. SCS has been utilized for decades to treat a number of pain etiologies, and continues to provide clinical benefit for a number of different indications. SCS usage for the treatment of diabetic peripheral neuropathy is no different and the literature has shown that using SCS can greatly improve the patient's pain, improve their quality of life, and even reduce their analgesic and opioid use.

Studies have shown that when using SCS therapy, pain relief is reduced on average over 60% in both the short term and long term. The improvement in pain relief is often accompanied by improvement in quality of life which was demonstrated in several studies. These two endpoints demonstrate that once SCS is used to treat DPN, the patient can return to a normal quality of pain free life, which is not due to increase medication. The long term benefit of SCS use has also been shown through these studies for both pain relief and quality of life.

[130] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021446s035,022488s013lbl.pdf
[131] https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022516lbl.pdf
[132] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/200533s023lbl.pdf

The two main sources of uncertainty that are associated with the evidence to support benefit are the influence of confounding factors such as medications, and the variability of the study designs included in the systematic review. With respect to medication usage, there is no evidence to suggest that there is any difference in the influence of medication usage for a DPN population compared to other pain etiologies for which SCS is approved. These patients will generally continue to remain on at least some medications, and perhaps the best indicator that the influence of those treatments is minimal is that in general, patients treated with SCS are decreasing their overall medication intake rather than increasing. With regards to the nature of the systematic review, there is expected to be some variability in the study designs, as they have been conducted by a number of different organizations for a variety of purposes. However, the combined evidence from these studies describes a consistent patient population, and consistently describes the clinical benefits that are experienced.

For intractable pain as a result of DPN, 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 DPN to conventional medical management, most patients, as shown above, experienced clinically meaningful reduction in pain symptoms, and those that do experience relief generally do so beyond the primary endpoints of the studies. When evaluating the risks associated with SCS in DPN patients, the adverse events and risks associated with SCS were generally consistent with the overall population, not just DPN patients. The one major exception was infection, however, there has been no data that associates infection with the use of SCS specifically for DPN. Given the lack of effective treatments for patients with DPN, clinical data has demonstrated that SCS offers a safe and effective option for the treatment of DPN where the benefits outweigh the risks associated with the therapy.

Published literature detailed above describing SCS to treat DPN provides information on specific inherent risks for the diabetic patient in the delivery and management of SCS therapy. This includes 2235 patients across 16 studies which reported on safety and adverse events in an identifiable diabetic population. With the exception of infection, the rates of common adverse events in the DPN population were similar to that of the general SCS population. Additional risks include, but are not limited to, 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, and/or by the use of appropriate surgical techniques and procedures.

Rates of infection were generally greater in DPN patients compared to the general SCS population in the RWE pulled from Medicare Claims data. Specifically, the number of device specific infections and those associated with a post-operative device related surgeries are not significantly higher in SCS patients with DPN as compared to the general SCS population.

The options that are currently available for the treatment of DPN beyond the management of a patient's glycemic control consist only of palliative treatments, which are largely pharmaceutical in nature. 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 comprehensive review of available data on the risk profile of the therapy in DPN 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. There is evidence from the literature to support the addition of language in the labeling that is specific to the population of pain patients with DPN, such that patients can be properly selected and managed particularly in the perioperative phase. These patients have relatively few treatment alternatives, and for patients without contraindications, SCS offers an 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.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for an Abbott 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 DPN 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 indications for use.

The options that are currently available for the treatment of DPN beyond the management of a patient's glycemic control consist only of palliative treatments, which are largely pharmaceutical in nature. 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 comprehensive review of available data on the risk profile of the therapy in DPN 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. There is evidence from the literature to support the addition of language in the labeling that is specific to the population of pain patients with DPN, such that patients can be properly selected and managed particularly in the perioperative phase. These patients have relatively few treatment alternatives, and for patients without contraindications, SCS offers an option for the treatment of intractable DPN where the benefits outweigh the risks associated with the therapy.

XII. CDRH DECISION

CDRH issued an approval order on January 24, 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).

XIII. 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.

XIV. References

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