SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: Saluda Medical Evoke® SCS System

Device Product Codes: LGW, QRB

Applicant's Name and Address: Saluda Medical Pty Ltd.
5 Eden Park Drive
Macquarie Park, NSW 2113
Australia

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P190002/S019

Date of FDA Notice of Approval: March 20, 2024

The original PMA (P190002) for the Evoke Spinal Cord Stimulation (SCS) System ("Evoke System") was approved on February 28, 2022, 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, 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 indications for the Evoke System to include painful diabetic peripheral neuropathy (DPN) of the lower extremities for open-loop stimulation for frequencies 1200 Hz and below.

II. INDICATIONS FOR USE

The Saluda Medical Evoke SCS System 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
- Diabetic peripheral neuropathy of the lower extremities

III. CONTRAINDICATIONS

The Evoke SCS System should not be used in patients who:

- Do not receive effective pain relief during trial stimulation
- Are unable to operate the Evoke SCS System
- Are unsuitable surgical candidates

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Saluda Medical Evoke System labeling. Safety information was updated using 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.

Please note the following regarding the diabetic peripheral neuropathy indication:

- The physiologic closed-loop controlled (PCLC) stimulation mode has not been evaluated for effectiveness in the diabetic peripheral neuropathy (DPN) population.

- Frequencies greater than 1200 Hz have not been evaluated for effectiveness in the diabetic peripheral neuropathy (DPN) population.

V. DEVICE DESCRIPTION

A. System Description

The Saluda Medical Evoke System is a rechargeable, upgradeable, multi-programmable, implantable, physiological closed-loop controlled neurostimulation system that delivers electrical stimulation to the spinal cord. The system consists of the following main components:

- **Closed-Loop Stimulator (CLS)** - The CLS is a rechargeable, 25-channel physiologic closed-loop controlled implantable pulse generator (IPG or stimulator) which generates an electrical stimulus and measures and records the nerve fibers' response to stimulus (i.e., ECAPs). It has a lithium-ion rechargeable battery and connects to two 12-contact leads. Although named "Closed Loop Stimulator", this stimulator delivers both open-loop and closed-loop stimulation modes.
- **External Closed-Loop Stimulator (eCLS)** – The eCLS provides stimulation by emulating the CLS during the intraoperative test and during the stimulation trial. The eCLS stimulation parameters are the same as the CLS.
- **Lead and Lead Extension** – The lead delivers electrical stimulation to the targeted nerve through electrodes on the end of the lead. ECAPs are measured using non-stimulating electrodes on the lead. The lead extension connects the lead to the stimulator (CLS or eCLS) if additional length is required.
- **Clinical Interface** (CI) – The programming system used by the clinician to program output stimulation parameters and measure and record ECAP signals. It is an off-the-shelf tablet computer installed with proprietary Saluda Medical software to allow programming of the CLS, eCLS, as well as data collection and analysis.
- **Evoke Patient Controller (EPC)** – The EPC allows patients to adjust stimulation within clinician-prescribed program limits stored on the stimulator (CLS or eCLS). Adjustments include starting and stopping stimulation, increasing and decreasing stimulation intensity, and toggling between stimulation programs.
- **Charger** – A battery-operated unit used to inductively charge the implanted stimulator (CLS) transcutaneously. The Charger battery is non-removable and rechargeable.

For additional details, refer to the Evoke SCS System manuals found at https://www.saludamedical.com/manuals.

B. Principles of Operation

Spinal cord stimulation (SCS) consists of applying an electrical stimulus to the spinal cord via electrodes implanted in the epidural space, which causes the activated fibers (e.g., Aβ-fibers) to generate action potentials. Aβ-fibers are the low-threshold sensory fibers in the dorsal column that contribute to inhibition of pain signals in the dorsal horn (1). The action potentials summed together form the electrically evoked compound action potential (ECAP). Therefore, ECAPs are a direct measure of spinal cord fiber activation that generates pain inhibition for an individual.

The Evoke System is designed to operate in either of two modes: open-loop (fixed-output) stimulation mode or physiologic closed-loop controlled (PCLC) stimulation mode using ECAPs. The open-loop stimulation mode is equivalent to other commercially available SCS systems but has an additional feature to measure ECAPs. The Evoke System has the ability to measure ECAPs following every stimulation pulse from two electrodes not involved in stimulation. The recorded ECAP signal is sampled by the stimulator and processed to allow measurement of the ECAP amplitude. ECAP measurement may be performed in either stimulation mode. Additionally, the Evoke System uses ECAPs as a feedback mechanism in PCLC stimulation mode. The feedback mechanism minimizes the difference between the measured ECAP amplitude and the ECAP amplitude target (set by the clinician and adjusted by the patient using the pocket console) by automatically adjusting the stimulation current for every stimulus. In doing so, it maintains spinal cord activation near the target level (Figure 1).

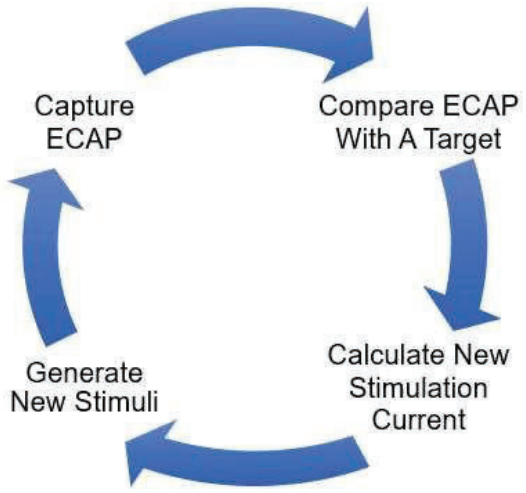

Figure 1. Evoke System Physiologic Closed-Loop Controlled Stimulation using ECAPs

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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 typically the primary approach to pain management through improved control of blood-sugar levels. In addition, pharmacologic treatments may be 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 be evaluated before selecting a first-line therapy.

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.

VII. MARKETING HISTORY

The Evoke System is currently approved for commercial distribution in Australia, the European Union, the United Kingdom, and the United States. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Evoke System.

Every surgery involves potential risks, including death. In addition to these surgical risks, the risks associated with the implantation and use of a spinal cord stimulation system include:

- Undesirable changes in stimulation sensation and/or location.
- Uncomfortable changes in stimulation (over and/or under stimulation).
- Temporary or persistent post-surgical pain at hardware implantation sites.
- CLS migration or suboptimal placement, which may result in pain or difficulty in charging.
- Seroma or hematoma at surgery sites.
- Epidural hemorrhage, spinal cord injury, possible paralysis or other neurological complications.
- Lead migration or suboptimal placement, which may result in undesirable stimulation changes.
- Breakage of the lead, or malfunction or failure of other system components, which may result in undesirable changes or loss of stimulation.
- Allergic response or tissue reaction to the implanted or external materials.

- Infection that may require hospitalization with intravenous antibiotic therapy.
- Infection may result in epidural abscess that can lead to neurological harm.
- Cerebrospinal fluid (CSF) leakage with possible fistula formation.
- Gastrointestinal and/or genitourinary disruption or compromise.
- Inadequate pain relief following system implantation over time.
- Erosion of the implanted components through the skin.
- Weakness, clumsiness, numbness, abnormal sensations, or pain.
- Skin irritation.

The patient may require surgery (including revision, explant, and replacement) as a result of any of the above.

For the specific adverse events that occurred in the supporting data, see Table 2 "Summary of Safety Results in Selected Studies" and section X.D.1 below.

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical bench and animal studies previously submitted in the Original PMA application (P190002) and supplements continue to support the safety of the commercially available Evoke System. No additional nonclinical studies were required to evaluate the safety of Evoke SCS therapy for the treatment of diabetic peripheral neuropathy (DPN) of the lower extremities.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The Evoke System is indicated 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 the Evoke System has been previously established for the approved indications (see Section I).

The clinical evidence supporting the safe and effective use of the Evoke System in the diabetic neuropathy population is based on a systematic review of published clinical scientific literature of commercially available SCS systems. Primary evidence comes from two randomized controlled trials in patients with diabetic peripheral neuropathy (DPN). Additional supplemental clinical evidence for safety was identified through the analysis of Evoke System clinical study safety data, investigating adverse event data related to the use of the Evoke System in patients with diabetes.

A. Study Design

The safety and effectiveness of the Evoke 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, Saluda Medical also analyzed clinical study safety data from diabetic patients implanted with the Evoke System. 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 the Evoke System to treat DPN was characterized through analysis of published scientific literature and clinical study safety data from patients implanted with the Evoke System. 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 clinical study safety data of the Evoke System 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 the Evoke System 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).

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

B. Evoke System Clinical Study Safety Data

Two Investigational Device Exemption (IDE) studies have been conducted evaluating the Evoke System to treat patients with chronic trunk and/or limb pain. The Evoke Study (NCT02924129), which is complete with 134 enrolled subjects, was a multicenter, double-blind, randomized controlled trial (RCT) with 36-month follow-up. The ECAP study (NCT04319887), which is ongoing with 300 enrolled subjects, is a prospective, multicenter, single-arm study with 24-month follow-up. The safety data for subjects enrolled in these studies who had diabetes were evaluated.

Data Selection

Subjects enrolled in the Evoke and ECAP studies were categorized into two cohorts: 1) Diabetes: patients with diabetes, and 2) non-Diabetes: patients without diabetes. The incidence of related adverse events up to 36 months following implantation were compared between the two cohorts to determine whether patients with diabetes who were implanted with SCS exhibited an increased risk of related adverse events when compared to the general population

of SCS patients. For both cohorts, the incidence of subsequent surgical interventions (i.e., device revision, replacement, or explant) following implantation were also evaluated.

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.

Two separate systematic searches and reviews were conducted. For both searches, the publications identified from databases were assessed for inclusion in the review through two 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 two 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: 1984-2023
    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: 2017-2023
    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

Clinical practice guidelines for perioperative care of diabetic patients

Initial screening was performed on 233 titles and abstracts resulting in the selection of 57 publications for full-text review. After full-text review, 30 publications were selected for inclusion. Guidelines are summarized in Table 1.

Table 1. Selected Guidelines

Author and Title	Summary	Recommendations	Noted Complications
American Diabetes Association Professional Practice Committee. 16. Diabetes Care 2022 (2) 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 hours 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 (3) 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 the night before surrey. • 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 HbcA1c < 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

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 (4) 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. 202 (5) 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-	• Postoperative hyperglycemia • Wound Infection • Acute renal failure

Author and Title	Summary	Recommendations	Noted Complications
		transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, should be considered as part of the 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 (6) 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 the time of surgery. • Diabetic patients should be identified early in pre-operative pathway. • Tests for comorbidities should be conducted including electroconvulsive therapy (ECT), urea and electrolytes for all patients. • Surgery should be scheduled early in the day to avoid disruption of glycemic control.	Autonomic neuropathy can cause perioperative hemodynamic instability
Cheisson et al. Anaesthesia, critical care & pain medicine. 2018 (7) 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	• 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.	• Infections • Delayed wound healing • Increased morbidity and mortality

Author and Title	Summary	Recommendations	Noted Complications
	the French society for the Study of Diabetes	• Replace insulin pump with immediate IV management during procedure. • Monitor glucose every 1-2 hours and potassium every 4 hours if under insulin control, and consider 3.8 mmol/L hypoglycemia requiring intervention. • All solutes may be used, including Ringer's lactate, in the peri-operative period. • Peri-operative control is dictated by 3 factors: diabetes type, pre-operative control, and type of surgery. • Manage risk of nausea and vomiting 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 (8) 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 (9) 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 the morning of surgery. • Long and intermediate acting insulin should be taken at 75-100% and 75% respectively the evening prior to the surgery day.	• Postoperative nausea and vomiting • Compromised wound healing • Postoperative glycemic stability

Author and Title	Summary	Recommendations	Noted Complications
		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. • Diabetic patients should be treated as the first patient early in the morning	
Dortch et al. Aesthetic Surgery Journal. 2016 (10) 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 (11) 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%).	• Microvascular complications

Author and Title	Summary	Recommendations	Noted Complications
		• 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.	
Galway et al. World J Diabetes. 2021 (12) Perioperative challenges in management of diabetic patients undergoing non-cardiac surgery.	Provides management guidelines for pre-operative assessment and management for non-cardiac surgery diabetes patients in the pre-operative, intraoperative, and post-operative phases	• In the preoperative phase, target Hba1c should be less than 8%. It is also recommended that the patient's 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 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.	• Postoperative complications: diabetic ketoacidosis, and hyperglycemic hyperosmolar nonketotic state • Acute renal failure, acute myocardial infarction • Longer ICU and hospital stay
Grant et al. Clinical Medicine, Journal of the Royal College of Physicians of London. (13)	Practice guideline focusing on the perioperative management of	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.	• Surgical related infection • Raise plasma glucose levels • Increase insulin resistance

Author and Title	Summary	Recommendations	Noted Complications
New guidance on the perioperative management of diabetes.	diabetic patients from the UK's Center of Perioperative Care (CPOC)	Before Surgery - Assess and Optimize • Diabetes • Comorbidities - 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 T1D are never denied insulin. 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,	• Diabetic ketoacidosis (DKA) • Hyperosmolar hyperglycemic state (HHS) • Hyper- or hypoglycemia

Author and Title	Summary	Recommendations	Noted Complications
		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 minimum 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 (14) Congress of Neurological Surgeons Systematic	This evidence-based guidelines provides a Grade B recommendation regarding HbA1c levels in diabetic	• 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

Author and Title	Summary	Recommendations	Noted Complications
Review and Evidence-Based Guidelines for Perioperative Spine: Preoperative Surgical Risk Assessment	patients undergoing spine surgery.		
Jinjing et al. Diabetes Metab Res Rev. 2021 (15) 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 patient's 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 consultation for patients with preoperative acute complications or severe chronic complications of diabetes. • Endocrinologist consultation 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 hours 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.	• Surgical site infection • Edema • Prerenal renal insufficiency

Author and Title	Summary	Recommendations	Noted Complications
		• 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 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 every1-2 hours intraoperatively and every 2-4 hours 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 hours intraoperatively and postoperatively every 2-4 hours. • 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 hours intraoperatively and postoperatively every 2-4 hours. • 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 hours and postoperatively every 4-6 hours. • 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 hours (2C).	

Author and Title	Summary	Recommendations	Noted Complications
		• Strengthen staff awareness of the importance 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's 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 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 24 hours before surgery. For patients with abnormal renal function, metformin should not be taken 48 hours before surgery, and not restarted until renal function is normal. • All staff administering insulin should be properly trained. • Use of insulin perioperatively is allowed and 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 hours of administration. For diabetic patients receiving NSAIDs	

Author and Title	Summary	Recommendations	Noted Complications
		(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 a 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 be integrated into physician training.	
Kheniser et al. J Diabetes Complications. 2018 (16) Diabetes management before, during, and after bariatric and metabolic surgery	Provides guidelines for pharmacological regimens during the preoperative to postoperative period for diabetic patients undergoing metabolic/bariatric surgery.	• 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. • 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 a 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. • A 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.	• Hypoglycemic and hyperglycemic episodes • Diabetic ketoacidosis (abdominal pain, nausea, vomiting)

Author and Title	Summary	Recommendations	Noted Complications
Kuzulugil et al. Curr Opin Anaesthesiol. 2019 (17) 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)
Leung et al. Health Serv Insights. 2017 (18) Perioperative Management of Patients with Diabetes	Perioperative guideline on assessment and management of diabetic patients and in regards to 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	• Hyperglycemia • Postoperative infection • Poor wound healing • Increased mortality • Metabolic derangements • Diabetic ketoacidosis (DKA)

Author and Title	Summary	Recommendations	Noted Complications

		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 discontinuing oral and noninsulin injectable medications.
		  ○ SGLT-2 inhibitors may increase the 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 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 hours after first dose of subcutaneous insulin to prevent gap in insulin coverage. For 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 should be given.	

Author and Title	Summary	Recommendations	Noted Complications
Livshetz & Nett. Tech. Orthop. 2019 (19) 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 result 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 (20) 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	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 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 (21)	Peri-operative guidance on peri-operative diabetes	• Pre-operative evaluation should include history, kidney function, blood count and coagulation profile, updated HbA1c.	• Increased postoperative morbidity and mortality

Author and Title	Summary	Recommendations	Noted Complications
Perioperative management of diabetes and corticosteroid supplementation	management and supplemental corticosteroid treatment	• 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.	
Robinson et al. Anaesth. Intensive Care Med. 2020 (22) 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 the 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). • Patients should be provided with information on managing their diabetes upon discharge.	• Post-operative infection (surgical site or systemic) • Cardiovascular events • Acute kidney injury • Stroke
Roth et al. Interdisciplinary Diabetes and Nutrition in Operative Intensive Care Medicine Competence Group. Dtsch Arztebl Int. 2021 (23)	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).	• Wound/systemic infections • Immune dysfunction (impaired leukocyte function and phagocytosis)

Author and Title	Summary	Recommendations	Noted Complications
Blood Sugar Targets in Surgical Intensive Care—Management and Special Considerations in Patients With Diabetes		• 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.	• Oxidative tissue stress, mitochondrial aberration, endothelial dysfunction • Hemodynamic effects (osmotic diuresis/ dehydration, volume depletion, hypoperfusion, electrolyte/acid-base balance disorders
Simha & Shah. JAMA. 2019 (24) 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 checked 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
Song et al. Endocrine. 2019 (25) 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 (26)	Peri-operative guidance on checking and managing blood	• Peri-operative screening in all patients with >200 mg/dL, further screened for HbA1c. • Goal of <7% HbA1c, though may be higher with individual cases.	• Delayed wound healing • Deep infection

Author and Title	Summary	Recommendations	Noted Complications
Modifying Risk Factors: Strategies that Work Diabetes Mellitus	glucose in patients with and without diabetes diagnosis undergoing total joint arthroplasty.	• 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.	• Thrombosis • Mortality
Vervoort et al. J Card Surg. 2022 (27) 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 24 hours 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 are not contraindications. • 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.	• Sepsis

Author and Title	Summary	Recommendations	Noted Complications
		• 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 (28) 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 (29) 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, psychosocial aspects, and frailty.	• HbA1c goal of < 7% • Pre-prandial glucose 90-130 mg/dL • Post-prandial glucose < 180 mg/dL • First-start surgical case (early in the surgery day). • Insulin Glucose Tolerance Test (GTT), IV management perioperative) for >200 mg/dL. • Continue home insulin, discontinue atypical hyperglycemic agents. • Cancellation of procedure if in diabetic ketoacidosis or >400 mg/dL.	• Delayed wound healing • Infection • Thrombosis • Mortality
Seisa et al. Journal of Clinical Endocrinology and Metabolism, 2022 (30)	This article supports the development of clinical practice guidelines for	• Continuous glucose monitoring. • Combine neutral protamine hagedorn (NPH) and basal-bolus insulin. • Emphasize inpatient diabetes education.	• Length of hospital stay • Hypoglycemia and hyperglycemia events • Hospital readmissions

Author and Title	Summary	Recommendations	Noted Complications
A Systematic Review Supporting the Endocrine Society Clinical Practice Guideline for the Management of Hyperglycemia in Adults Hospitalized for Noncritical Illness or Undergoing Elective Surgical Procedures.	management of hyperglycemia in adults hospitalized for noncritical illness undergoing elective surgical procedures.	• Achieve preoperative HbA1c level < 7% when possible. • Hospitalized patients with type 2 diabetes and mild hyperglycemia can be treated with glucagon-like peptide-1 agonists or dipeptidyl peptidase-4 inhibitors if indicated. • All findings were associated with a low or very low level of certainty. Additionally, several factors supported opposite recommendations depending on the outcome measured. This emphasizes the need for shared decision making and consideration of all available factors.	
Williams et al. Journal of Patient Centered Research Reviews, 2023 (31) Impact of Perioperative Dexamethasone on Hospital Length of Stay and Glycemic Control in Patients With Type 2 Diabetes Undergoing Total Hip Arthroplasty.	Evaluation of length of hospital stay in patients with type II diabetes when prescribed dexamethasone perioperatively.	• Dexamethasone can be safely administered to patients with type II diabetes during surgical procedures to relieve subsequent pain and nausea. • Those taking insulin may benefit from having their postoperative care managed by diabetes specialists due to increased insulin resistance in the first 24 hours following surgery.	• Elevated blood glucose levels

Safety and Effectiveness Literature Search

Initial screening was performed on 690 titles and abstracts resulting in the selection of 133 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: 26 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 2.
- Effectiveness: 15 publications. Several studies resulted in multiple publications. Effectiveness data was extracted from all publications and included in total for each cohort. This information is reported in Table 3**.**
- Meta-analyses: 8 publications reported meta-analyses of studies of SCS to treat DPN. The reports are summarized in Table 4.

Table 2. Summary of Safety Results in Selected Studies

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
Tesfaye et al. 1996 (32), Daousi et al. 2005	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 (33)	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-up times variable, no separate DPN population. No analysis of diabetes related to SCS complications.
Petrakis et al. 1999 (34)	Retrospective study of diabetic patients with peripheral arterial occlusive disease (PAOD) to evaluate pain relief and reduction of amputation rate with SCS	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. Overall diabetic cohort had 8 battery replacement procedures following normal end of device life, 2 lead migrations requiring lead revision, 2 Infections requiring explant.	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.
de Vos et al. 2009 (35)	Prospective, open label, observational trial for diabetic patients with	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	Relevance: Few safety events which were resolvable. Limitations: Open label design. Single center, small trial without comparator.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
	chronic pain			antibiotics, without any influence on the SCS treatment. One death which was reported as unrelated to SCS.	
Mekhail et al. 2011 (36)	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.
Pluijms et al. 2012 (37), Pluijms et al. 2015 (38), Slangen et al. 2013 (39), Slangen et al. 2014 (40), van Beek et al. 2015 (41), van Beek et al. 2018 (42) Zuidema et al 2022 (43)	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 PDPN in the lower limbs. Patients were pooled from all subjects reported in Pluijms 2012	49 patients enrolled 40 patients had a successful trial and received a permanent implant 19 continued use of the device at 8 or more years and consented to participate in the study	Up to 10 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 explant • 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 • During the 8-10 year follow-up, many patients needed either one (53%) or two (24%) replacements the original non-rechargeable IPG • There were no new AEs reported in the 8-10	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 10 years. Many device explants happened in the first two to three years; however, after this period, device explants were less frequently observed. The ten-year survival probability was equal to 0.66 (95% CI: 0.53–0.83). Limitations: Open label. No control group for the 5- or 10-year follow-up period. Study enrollment over 4 years, potential for increased expertise in

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
	and Slangen 2014			year follow-up	surgeons or nurses who implant or change SCS settings.
de Vos et al. Feb 2014 (44)	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 (45)	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 into 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 coronary bypass surgery.	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 was biased by this prospect.

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
Bir et al. 2016 (46)	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 (47)	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 (48)	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 16.5% 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%. Analysis of surgical site infection association with diabetes. Infection rate for patients with diabetes: 1.99% without diabetes: 2.54% (p = 0.49)	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 the 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 of continuity for some of the categorical variable data related to inconsistent reporting.
Falowski et al. 2019 (49)	Retrospective analysis of patients with SCS implant from 2009-2014 included in a payer	26,854 patients had a record of SCS generator implant or replacement during the study period. The final study	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	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

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
	database to estimate rates of infection and other safety risk factors.	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).		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. There was no difference in the rate of diabetes between those that had infections and those that did not.	between those that had infections and those that did not. Limitations: Uncertainty in the results stems 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.
Galan et al. 2020 (50)	Patients with DPN were reported 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 implant site dehiscence • 1 leg pain • 1 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 independently with detailed AE information. Limitations: Post-hoc analysis, limited samples size, therefore no statistical analyses performed. Adverse event rates are difficult to assess due to the small sample size.
Antonovich et al. 2021 (51)	Single center, retrospective analysis of SCS reoperation rates for leads (paddle vs percutaneous).	291 patients 67% had a history of back surgery, 22.34% had diabetes	Up to 10 years	89 patients required 1 revision (31.58%), 20 required 2 or more revisions (1.72%) 35.59% of participants with paddles needed revision, 47.17% of participants with cutaneous leads needed revision Overall infection rate of 1.95%. Paddles were associated with 3x higher rates of infection.	Relevance: Large data set that analyzed diabetes as a co-factor. No association between diabetes and lead/paddle type in time to re-operation. Use of leads associated with lower infection rates in the general SCS population. Limitations: Single center, retrospective study. No detailed AE data for diabetic population. Study reported a potential for

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
				A diagnosis of diabetes was not associated with reoperation (univariate Hazard Ratio = 0.70; p = 0.197).	charting errors, misinterpretation of charts, errors gathering data.
Petersen et al. 2021 (52), Petersen et al. 2022 (53) Peterson et al 2022 (54)	Prospective, multi-center, open label, randomized trial 10kHz stimulation was compared with conventional medical management 12 month follow-up data included in two secondary publications (Petersen et al., 2022 and Petersen et al., 2022)	216 patients were randomized at 1:1 ratio (103 control group and 113 in the treatment group) 104 patients had a trial stimulation, 90 subjects received a permanent implant 187 patients completed 6-month follow-up visits	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 treatments and patients continued in the study, five (3.2%) required device explant with 1 receiving a new implant after the infection resolved • 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., explant)	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 not. Limitations: It is unclear if multiple adverse events occurred in the same patient and limited information is provided on the reasons for explant. Long-term follow-up was open label.
Goel et al 2022 (55)	Retrospective analysis of reasons for SCS related hospital readmission	3,668 patients from the National Readmissions Database (NRD) were included	30 days	• The 30-day readmission rate following the SCS implantation procedure was 7.7%. • Readmissions for uncontrolled diabetes accounted for 2.38% of all admissions • A univariate analysis determined that diabetes was a significant predictor for readmission generally (OR - 1.484, p=0.020).	Relevance: Evaluates reasons for readmission within 30 days of SCS implantation in 3,668 patients in a database that pulls from 28 states. Uncontrolled diabetes was recognized as a factor that contributed toward readmission rates generally but was not a predictor of readmission following SCS surgery. Limitations: Focus on all SCS implantation, no data reported for a DPN population alone. Limited follow-up. Many revision surgeries happen in the first two years, so this evaluates a percentage of the population that has

Publication	Study Design	N	Follow-up period	Safety data	Relevance and Limitations
					revision surgeries.
Provenzano et al 2022 (56)	Retrospective study at a single center to determine the prevalence of *S. aureus* colonization for SCS surgical patients and to identify specific at-risk patient populations.	232 patients underwent 396 unique neuromodulation procedures	Minimum 6 months	• Patients were screened for *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) prior to surgery. • 23.3% of patients were colonized with *S. aureus* (4.3% with MRSA and 20.2% for MSSA) • No postprocedural SSIs were identified. • The only co-morbidity that was significantly associated with MRSA colonization was anxiety, and hypothyroidism was the only co-morbidity associated with MSSA MRSA: methicillin-resistant *S. aureus* MSSA: methicillin-sensitive *S. aureus*	Relevance: Large data set that analyzed diabetes as a co-factor. No association between diabetes and *S. aureus* colonization. Many of the previously associated risk factors/co-morbidities did not show an association with MRSA or MSSA colonization. Limitations: Single center, retrospective study. No patients in this study had surgical site infections, so no conclusions can be made for the diabetic patient population.

Table 3. Summary of Effectiveness Results in Selected Studies

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
Tesfaye et al 1996 (32); Daousi et al 2005 (57)	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). 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).	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.
de Vos et al. Feb 2014 (44)	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. Several patients indicated that they actually liked the paresthesia. The loss or change of the	Relevance: First assessment of switching 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 despite meaningful additional pain relief.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
				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. Success criteria were not established.	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.
de Vos et al. Nov 2014 (45), Duarte et al. 2016 (58)	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.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
Slangen et al. 2014 (40), van Beek et al. 2015 (41)	Prospective, randomized, open-label, multicenter RCT to assess the effectiveness of SCS in combination with best medical treatment (BMT) compared with BMT alone in patients with DPN in the lower limbs.	36 randomized patients (22 for SCS and 14 for BMT) 17 of 22 had a positive trial period and went on to permanent SCS implantation. 1 withdrew after infection and removal of the SCS implant.	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 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).	Relevance: RCT to compare SCS against BMT. Includes BMT patients who were able to crossover to the SCS arm. Multicenter. Data shows meaningful effects in pain reduction over a 2 year follow-up. Limitations: Open label. No control group for the 2-year follow-up period.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
de Vos et al. 2009 (35)	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%) • 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%.	Relevance: Good long-term effectiveness seen in patients. Limitations: Open label design. Single center, small trial without comparator.
Pluijms et al. 2012 (37), Pluijms et al. 2015 (38), Slangen et al. 2013 (39)	Prospective, open-label, single center cohort study on the use of SCS in patients 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. Overall success rates were 67% of patients (10 of 15) after 1 year of SCS treatment, 40% (6 of 15) at 24 months and 47% (7	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.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
				of 15) at 36 months*. 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 (34)	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.
van Beek et	Multi-center cohort	49 enrolled patients, 40	5 years	Adjusted NRS pain score reductions of 50% or	Relevance: 5-year follow-up of two

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
al. 2018 (42)	study of SCS to treat DPN with analyses of predictors of success. Combined cohorts from Puijms 2012[7] and Slangen 2014[10]	patients received a permanent implant.		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).	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.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
Kumar et al. 1996 (59)	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.
Zuidema et al 2022 (43)	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 PDPN in the lower limbs. Long term follow-up of Pluijms 2012 and Slangen 2014	40 patients received a permanent implant, and 19 continued to use the device at 8 or more years and consented to participate in the study	8 – 10 years	Mean NRS scores for pain intensity during the day and night significantly decreased by 2.3 ± 2.5 and 2.2 ± 2.4 points, respectively, compared to baseline. 57.9% (day) and 53.3% (night) of patients had ≥ 30% reduction in pain intensity. 26.3% (day) and 33.3% (night) of patients had ≥ 50% reduction in pain intensity. Stimulation pulse width widely ranged from 150 to 450 μm. For stimulation frequency, most patients (65%) were stimulated at the default frequency of 30 Hz, but higher frequencies up to 60 Hz were also used. Most patients (82%) needed a maximum of eight adaptations (maximum one per year) during the follow-up time. No differences were observed regarding the	Relevance: This is the first study with follow-up out to 10 years in more than a few patients. Long term efficacy is preserved in patients that do not fail in the earlier stages (first 1-2 years). Limitations: The only available data at this late time point was from a subset of patients that still have their SCS implanted at this stage. Open-label follow-up.

Publication	Study Design	N	Follow-up period	Effectiveness data	Relevance and Limitations.
				secondary outcomes (i.e., QoL, depression, sleep quality).	

Table 4. Summary of Safety and Effectiveness Conclusions in Selected Meta-Analyses

Publication	Study Design	N	Safety Conclusions	Efficacy Conclusions
Hou et al. 2016 (60)	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.	Not enough evidence to recommend for or against use of burst to treat chronic pain or DPN. More high-quality evidence is needed.
Raghu et al. 2021 (61)	Meta Analysis of neuromodulation for DPN. MEDLINE and Embase were searched for appropriate articles. Results were screened by 2 independent reviewers. RCT data 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.	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 was 13%: 4% per year of follow-up. IPG replacement was 0% at six months, 12% at two years, 17% at three years, and 45% at five years. Following "permanent" implantation, likelihood of explant was 20% by five years. One patient died from subdural hematoma.	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 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 (62)	Systematic Review 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,*

Publication	Study Design	N	Safety Conclusions	Efficacy Conclusions
				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.
Xu L, et al. 2022 (63)	Review of all non-pharmacologic treatment options for DPN; PRISMA guided literature search.	15 articles on the use of SCS for pain management 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 (64)	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 (65)	Review of 4 SCS studies in DPN	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. Patients achieving stoppage of analgesic usage: 67% at 1 year, 47% in the 2,5-3-year range, and 29% at 7 years.

Publication	Study Design	N	Safety Conclusions	Efficacy Conclusions
Duarte et al. 2022 (66)	Review of 4 SCS studies in DPN to evaluate superiority of different stimulation frequencies	LF-SCS: 96 patients were enrolled and randomized to SCS (n = 62) or control (n = 34) treatment. HF-SCS: 216 patients were enrolled and randomized to SCS (n = 113) or control (n = 103) treatment.	Treatment-related adverse events were reported narratively, but no safety related calculations or conclusions were made. No new safety data.	There was a significantly greater reduction in pain intensity on HF-SCS compared to LF-SCS at 6 months (MD -2.07, 95% CI -3.26 to -0.87, moderate certainty). There were no significant differences at the 3-month time point between HF- and LF-SCS.
Hoelzer et al 2022 (67)	Meta-analysis that compared safety and efficacy between 2 low-frequency and 1 high frequency studies for the treatment of DPN at six months post implantation	LF-SCS: 96 patients were enrolled and randomized to SCS (n = 62) or control (n = 34) treatment. HF-SCS: 216 patients were enrolled and randomized to SCS (n = 113) or control (n = 103) treatment.	Treatment-related adverse events were reported narratively, but no safety related calculations or conclusions were made. No new safety data.	HF-SCS achieved statistically significant increases in pain reduction compared to LF-SCS ($p<0.0001$). 72.12 % of all HF-SCS patients were responders, and 54.84% of LF-SCS patients were responders ($p=0.018$). If you compare only patients that received a permanent implant, 83.33% of HF-SCS patients were responders, and 62.96% of LF-SCS patients were responders ($p=0.0072$).

D. Safety and Effectiveness Results

1. Safety Results

Clinical practice guidelines on the perioperative care of diabetic patients

Recommendations on the perioperative care of diabetic patients were extracted from the individual publications. Seventeen (17) of 30 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 ranged 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 a 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.

From the selected clinical guidelines, referenced articles describing incremental risks were reviewed for rates of perioperative complications as well as relative risk levels (described as Odds or Hazard Ratios) in the diabetic population. The sources were screened for similarity of populations studied as compared to SCS (elective, orthopedic or spinal surgery, etc.). A summary is provided in Table 5. Most noted perioperative events were more likely to occur in diabetic patients with higher HbA1c levels, with odds ratios ranging from 1.17 to 6.07. Of the data sources reviewed, diabetic patients were twice as likely to have an infection with delayed wound healing possibly contributing to this risk being 6 times more likely in patients with higher HbA1c levels (Han et al, 2013) (68). Myocardial infarction was 1.5 times more likely to occur in uncontrolled diabetic patients based on a univariate analysis but did not reach significance in the multivariate analyses (Marchant et al. 2014) (69). Stroke risk was also elevated in the same cohort (Marchant et al. 2014) (69).

Additional references provided information on the risk of CSF leaks and subdural hematomas in diabetic patients. Ha et al. 2016 reported data from a non-SCS procedure (craniotomy) 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 a significant relation between diabetes and CSF leak (Odds Ratio = 1.82; $p = 0.448$) (70). The more invasive nature of a craniotomy compared to SCS lead placement limits the applicability of this concern to SCS procedures. Wang et al. 2014 reported increased incidence of subdural hematoma in diabetic patients (log-rank test, $p<0.0001$) (71). This analysis considered all causes of

subdural hematoma, including traumatic and non-traumatic events. Cox proportional hazard modeling resulted in an adjusted Hazard Ratio = 1.63. In addition, as explanations for this increase in relative risk, the authors hypothesized that the prevalence of cardiovascular disease and subsequent use of anti-coagulants as well as renal disease may contribute to increases in bleeding tendency or that brain atrophy and subsequent stretching of bridging veins increases the likelihood of vessel tearing.

Table 5. 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) (68): 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) (72): 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) (73): Lumbar fusion surgery, Infection rate = 0.68%	Brown et al. (2007): OR = 1.52
	Anderson et al. (2017) (74): Spine surgery, Infection rate for highest risk groups undergoing laminectomy = 2.3%	Anderson et al. (2017): OR = 2.04
	Marchant et al. (2009) (69): Total Joint Arthroplasty, Infection rate = 0.38% in controlled diabetes and 1.18% in uncontrolled diabetes	Marchant et al. (2009): OR = 2.28
	Wang et al. (2020) (75): 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) (76): 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) (69): 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) (71): 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) (70): 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 (2).

Evoke System Clinical Study Safety Data

Available data on all 434 subjects enrolled in the Evoke and ECAP IDE studies of the Evoke System were included in the safety analysis; 87 subjects were diabetic and 347 non-diabetics. Adverse events adjudicated by the independent Clinical Events Committee (CEC) as possibly or definitely related to the procedure, device and/or stimulation therapy (i.e., 'related adverse events') occurring from the time of the trial procedure through up to 24-months (ECAP study) and 36-months (Evoke study) post-permanent implant were evaluated. The diabetic subjects had a mean of 21.5 months of device exposure, ranging from 1 to 2012 days.

A total of 14 related AEs occurred in 12 (13.8%) diabetic subjects. The results indicate a low incidence of related adverse events in diabetic patients with SCS, including incidence rates for the following common adverse events: 5.7% for lead migration, 2.3% for device site swelling or pain, 1.1% for hematoma, 1.1% for infection. There were no reports of CSF leak/dural tear, lead failure, or uncomfortable stimulation/stimulation issues in the diabetic subjects (Table 6). Furthermore, there was no statistical evidence of a difference between diabetic and non-diabetic subjects in the incidence of related adverse events (all $p \geq 0.20$). There was also no statistical evidence that the incidence of subsequent surgical procedures (i.e., revision, replacement, or explant) significantly differed between diabetic and non-diabetic subjects (all $p > 0.18$).

Additionally, Kaplan-Meier survival (freedom from event) analyses were performed comparing common related adverse events and subsequent surgical interventions between the diabetic and non-diabetic subjects enrolled in these studies. Infection, lead migration, lead failure, device site swelling or pain, hematoma, wound dehiscence, CSF leak/dural tear, uncomfortable stimulation/stimulation issues, revision, replacement, and explant were compared. The time course of events was generally similar with no significant differences for diabetic and non-diabetic subjects.

These results, taken together, suggest that the use of the Evoke System in the diabetic patient population does not lead to increased risk of device related adverse events or subsequent surgical procedures.

Published Literature – Safety

Common Adverse Events

Studies which included detailed adverse event information were pooled to assess common adverse event occurrences. Table 6 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 6. Common Adverse Events

			Adverse Event Counts (%)						
Study		**Sample Size** [t,i]	**Infection**	**Lead migration**	**Lead failure**	**Device site swelling or pain**	**Hematoma / Erosion / Wound Dehiscence**	**CSF Leak/ Dural tear**	**Uncomfortable stimulation / stimulation issues**
DPN	Petersen (2021, 2022, 2022)	104	8 (7.7)	1 (1.0)		2 (1.9)[c]	4 (3.8)		1 (1.0)
	Pluijms (2012) Slangen (2013, 2014) van Beek (2015, 2018) Zuidema (2022)	49	2 (4.1)	5 (10.2)	4 (8.2)	10 (20.4)		1 (2.0)[g]	9 (18.4)
	Galan (2020)	9				1 (11.1)[d]	1 (11.1)		
	de Vos (2014)	40	3 (7.5)[b]	1 (2.5)		2 (5)			2 (5)
	de Vos (2009)	11	1 (9.1)		2 (18.2)				
	Tesfaye (1996) Daousi (2005)	10	2 (20)	2 (20)	1 (10)		1(10)		
DM	Falowski (2019)	1663	59 (3.5)						
	Hoelzer (2017)	452	9 (2.0)						
	Mekhail (2011)	56	5 (8.9)						
	Petrakis (1999)	64	2 (3.1)	2 (3.1)					
Evoke System Clinical Studies[a]		87	1 (1.1)	5 (5.7)	0 (0.0)	2 (2.3)[e]	1 (1.1)[f]	0 (0.0)	0 (0.0)
Range			1.1%-20%	1.0%-20%	8.2%-18.2%	1.9%-20.4%	1.1%-11.1%	2.0%	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
t,i: Sample sizes reflect subjects exposed to either the trial stimulation or permanent IPG implant as described in the individual publications.
a: There were no reports of lead failure (i.e., lead breakage/fracture), CSF leak/dural tear, or uncomfortable stimulation/stimulation issues (i.e., overstimulation or unwanted stimulation location) in any of the diabetic patients enrolled in the IDE clinical studies of the Evoke System.
b: Two patients with infection also had fluctuations in their blood glucose levels.
c: IPG pain leading to location revision surgery

d: Based on report of implant site seroma
e: Rate of IPG pocket pain
f: Rate of hematoma; there were no reports of erosion or wound dehiscence in any of the diabetic patients enrolled in the IDE clinical studies of the Evoke System.
g: CSF leak reported in one subject during aborted trial lead placement and reported in Slangen (2014)

Published literature describing SCS to treat DPN and published clinical practice guidelines on peri-operative care of diabetic patients provides 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 a rate ranging from 1.1 to 20%. The incidence of infection in DPN and diabetic patients 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) (77). The results of the clinical studies of the Evoke System indicate that the incidence of related infections in diabetic patients is 1.1%, which falls below the 2-20% incidence range reported in the literature. Additionally, related infections were not significantly different between diabetic and non-diabetic patients (wound infection p-value = 1.000; non-specific infection p-value = 0.490). 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 (36,48,49). Therefore, the various sources of evidence are consistent and show DPN and diabetic patients 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.

  Infections were either resolved using solely antibiotics or through removal of the infected components of the SCS system followed by administration of antibiotics.

  The only complications as a result of infections explicitly mentioned in the literature include device explant, abscess formation, and changes in glucose level stability. Specifically, Peterson et al. (2022) reported that out of eight patients who had procedure- related infections, three were able to resolve the infection with conservative treatments with no specified complications, whereas five required surgical explant of the device (53). Another infection related complication is an increased risk of blood glucose fluctuations. This risk is highlighted by de Vos et al. (2014) in which two subjects experienced fluctuations in blood glucose levels in response to an infection (45). 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. Of note, the one infection that occurred in the clinical studies of the Evoke system did not result in device explant, abscess formation, or changes in glucose level stability that were noted.

- **Wound Healing Complications Including Hematoma, Erosion, Wound Dehiscence**

  Data on adverse events related to wound healing such as hematoma, erosion, and wound dehiscence in DPN and diabetic patients indicate a rate ranging from 1.1 to 11.1%. The results of the clinical studies of the Evoke System indicate that the incidence of hematoma, erosion, or wound dehiscence in diabetic patients is 1.1% (one report of hematoma; no reports of erosion or wound dehiscence in diabetic patients), which falls below the 3.8-11.1%

incidence range reported in the literature. Additionally, the rates of hematoma, erosion, or wound dehiscence were not significantly different between diabetic and non-diabetic patients (hematoma p-value = 0.490; wound dehiscence p-value 0.588; no reports of erosion in diabetic or non-diabetic patients).

Diabetes is known to be a potential risk factor for wound healing (e.g., hematoma, erosion and wound dehiscence), which can lead to infection. However, rates of these events may be underreported due to subsequent development of a more serious adverse event such as infection.

- **Cardiovascular events**

  Reports of subject or patient death attributed to myocardial infarction (n=3) or cardiac arrest (n=1) were reported in the published literature on SCS to treat DPN (45,57). However, 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), 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; $p < 0.001$) (69). There were no deaths due to a cardiac event in diabetic patients enrolled in the clinical studies of the Evoke System.

- **Dural puncture and CSF leak**

  Slangen et al. (2014) reported one death due to subdural hematoma after dural puncture during the attempted trial lead implantation (40). A review of the literature was conducted to identify publications that report CSF leak in patients with diabetes. Data from craniotomy procedures in Ha et al. (2016) and Hutter et al. (2014) suggest that diabetes may be a risk factor for CSF leaks (70,78). However, the more invasive nature of craniotomy procedures limits the generalizability of this concern to SCS procedures. Wang et al. (2014) 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] (71). There were no reports of dural puncture or CSF leak in diabetic patients enrolled in the clinical studies of the Evoke System.

- **Glycemic control**

  de Vos et al (2014) reported 2 subjects experiencing fluctuations in blood glucose levels following infections (45). While these were determined by authors to be 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) published a multi-center retrospectives study characterizing the morbidity and mortality of patients treated with SCS for refractory Angina Pectoris (33). 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.

As discussed above, Tesfaye et al. (1996) and Daousi et al. (2005) reported 3 deaths over the 7-year study period (32,57). 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) reported one death out of the 11 patients who enrolled in the study. The authors noted that the cause of death was unrelated to SCS (35).

de Vos et al. (2014) reported one case of prolonged hospitalization due to coagulopathy following the implant procedure (45). As discussed above, the publication also described one subject in the SCS group that experienced cardiac arrest unrelated to the study procedure.

As discussed above, Slangen et al. (2014) reported one death out of 22 patients assigned to the SCS treatment group due to dural puncture during implantation of the trial stimulation lead (40). 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.

One death due to kidney failure occurred in a patient enrolled in the clinical studies of the Evoke System who had a baseline history of diabetes and renal insufficiency. The event was determined to be unrelated to the SCS procedure, device, or stimulation therapy.

- **SCS-specific events**

  Device events may be associated with or the cause of certain adverse events. Several reports describe hardware-specific complication rates including SCS system survival, lead migration, and lead failure.

- **SCS system survival**

  Bir et al. (2016) reported 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 (46). 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) (51). Of note, the rate of device revision, replacement, or explant was not significantly different between diabetic and non-diabetic patients enrolled in the clinical studies of the Evoke System (revision p-value = 0.304; replacement p-value = 0.319; explant p-value = 1.000).

- **Lead migration**

Data on lead migrations in DPN and diabetic patients indicate a rate ranging from 1-20%. The incidence of lead migration in DPN and diabetic patients is comparable to overall rates of lead migration associated with SCS of 15.49% (range: 2.1 to 27%) as reported in a systematic literature review by Eldabe et al. (2016) (77). The results of the clinical studies of the Evoke System indicate that the incidence of lead migration in diabetic patients is 5.7%, which falls within the 1-20% incidence range reported in the literature. Additionally, lead migrations were not significantly different between diabetic and non-diabetic patients (p-value = 0.353).

- **Lead failure**

  Data on lead failure, including lead fracture/breakage or malfunction, in DPN and diabetic patients indicate a rate ranging from 8.2%-18.2%. The incidence of lead failure in DPN and diabetic patients is comparable to overall rates of lead failure associated with SCS of 6.37% (range: 0 to 10.2%) as reported in a systematic literature review by Eldabe et al. (2016) (77). The were no reports of lead failure in diabetic patients enrolled in the clinical studies of the Evoke System.

2. Effectiveness Results

Published Literature – Effectiveness

The evaluation of the effectiveness of the Evoke 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 15 publications from 8 studies reporting results applicable to evaluate the effectiveness of SCS for DPN (Table 3).

Non-comparative studies

Eleven (11) publications include data from 6 single-arm studies that evaluated the use of SCS to treat DPN (32,34,35,37–39,42–44,57,59). 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 10 years).

Comparative studies

Two (2) randomized controlled trials (RCT) investigated the use of SCS to manage pain from DPN; results from these studies were described in 6 publications (40–43,45,58). Table 7 presents a comparison of the two initial studies which reported on the primary outcomes.

Table 7. Details of publications describing randomized studies on DPN

Publication	**Slangen et al. 2014** (40)	**de Vos et al. 2014** (45)
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 Between 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 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 8.

Table 8. Comparison of study demographics

Demographic[a]	**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%

[a]Data are pooled for the SCS and Control groups and reported as weighted averages within each study.

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 9. Pain-related outcomes were similar between studies with 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 9. 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 standard-of-care with primary endpoints at 6 months, data from both studies were pooled and are presented in Table 10. Average values were weighted by the number of subjects in the respective SCS and Control treatment groups for each study.

Table 10. 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	6.6
Average 6-month pain rating	3.4	6.6
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 the 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 compared to standard-of-care. The overall mean log OR 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 for the treatment of DPN.

A second analysis based on a 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 11). 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 11. 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) (42) published long-term follow-up results for subjects from the studies reported by Pluijms et al (2012) (37) and Slangen et al (2014) (40). 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.

Zuidema et al (2022) published the results on the 19 subjects from this same cohort who had ≥8 (range 8-10) years follow-up (43). The authors observed that the efficacy stabilized after 5 years with consistent results out to 8-10 years follow-up.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was leveraged to support the reasonable assurance of safety and effectiveness of the proposed 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 years of age 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 2016.

Diabetic peripheral neuropathy is a condition that can occur in individuals who are 18-21 years of age. Jaiswal et al (2017) assessed the prevalence of DPN in pediatric populations with either type 1 or type 2 diabetes enrolled in a clinical study (79). 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 meets or exceeds a certain percentage 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 years of age 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 (80).

The Evoke 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 positioning of the device is the same for adults aged 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 the older than 22 years population. Therefore, there are no differences in the location or duration of implantation 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 Evoke System needs no modifications to be used for a patient aged 18-21 compared to those patients aged 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 is done currently. Similarly, the stimulation is set on an individual basis, and is not calibrated any differently for the 18-21 years of age 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 years of age with DPN and those who are aged 22 and older with DPN. Skeletal maturity is achieved by age 18, for example, and relative to a patient who is 22 years of age, 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 Evoke System will have previously been diagnosed with DPN, the process of which is the same for adults aged 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. Therefore, there are no differences in disease characteristics that could affect the safety or effectiveness of the device 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 years of age 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 Evoke 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.

XI. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The Original PMA (P1900002) SSED includes this information as required for the pivotal study. Of note, there was a single investigator with disclosable financial interests/arrangements included in the pivotal study; however, the diabetic subset supporting this PMA supplement does not include any patients from the site of this Investigator. The information provided does not raise any questions about the reliability of the data

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST PANEL ACTION

XIII. 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 supplement was not referred to the Neurological Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

A total of 15 publications from 8 studies (several publications reported alternative analyses or long-term follow-up) described effectiveness outcomes associated with SCS to treat DPN. Two RCTs comparing SCS to the standard-of-care included a total of 96 subjects, four prospective studies without a comparator included a total of 84 subjects, and two retrospective studies

contained data on 68 patients with diabetic neuropathy.

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 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. A meta-analysis of both studies resulted in an overall mean log OR of 3.21 (95% CI 1.68 to 4.73), corresponding to an Odds Ratio of 24.8 in favor of treatment success with SCS for the treatment of DPN.

Long-term efficacy data on subjects treated with SCS to treat DPN from one nonrandomized study and one RCT reflecting outcomes after 8-10 years of treatment showed a sustained pain relief at clinically meaningful levels.

There were an additional 8 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 all these studies support the effectiveness of the Evoke System for patients who suffer from chronic, intractable pain of the trunk and/or limbs, including pain from diabetic peripheral neuropathy of the lower extremities for open-loop stimulation at frequencies of 1200 Hz and below.

B. Safety Conclusions

The clinical evidence supporting the safety of the Evoke System to treat DPN includes a systematic literature review of published scientific literature reporting SCS to treat chronic intractable pain in patients with diabetes in general, and data from diabetic patients enrolled in IDE clinical studies of the Evoke System.

Safety data from 223 subjects across 6 studies treated with SCS for their DPN were included. An additional 2322 patients were included across 6 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 published literature on SCS to treat DPN and the published clinical practice guidelines on perioperative care of diabetic patients described some inherent risks for diabetic patients treated with SCS 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.

There were an additional 8 meta-analyses that independently reviewed safety information and determined that risks of SCS in the diabetic population were similar to the conclusions from the previously published studies.
Refer to the labeling for safety information and considerations specifically addressing the use of

the Evoke System in the diabetic population.

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 the feet, legs, or hands. It is the most common complication of diabetes.

About 60% to 70% of all people with diabetes 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 the patient's blood sugar within the target range. If the patient develops DPN, the primary treatments are for pain relief. Currently, medications such as anticonvulsants, antidepressants, and opioids are approved by the FDA for the treatment of diabetic neuropathy. Non-pharmacologic treatments (physical therapy, cognitive therapy, and transcutaneous electrical nerve stimulation [TENS]) should be provided in conjunction with first-line medical treatment. Often times, however, these options are no longer effective, and the patient needs other solutions to treat their DPN. 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 Evoke System is the improvement in pain, including for diabetic peripheral neuropathy. 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 for the treatment of diabetic peripheral neuropathy is no different and the literature has shown that SCS can greatly improve the patient's pain, quality of life, and even reduce their analgesic and opioid use.

Studies have shown the short- and sustained long-term benefit of SCS to treat DPN both through pain relief and quality of life improvements. Pain relief is reduced on average over 60% with SCS and is often accompanied by improvement in quality of life, which was observed in several studies. These two endpoints demonstrate that once SCS is used to treat DPN, the patient may return to a pain-free normal quality of life, without increased medication usage.

Sources of uncertainty that are associated with the evidence to support benefit include 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 tend to decrease their overall medication intake rather than increase it. 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. Additionally, the random and fixed effects analyses supported homogenization of the RCTs that demonstrated superiority of SCS versus standard-of-care to treat DPN. Limitations of the published literature data are that the studies were conducted using open-loop stimulation modes only, whereas Saluda's system also utilizes a closed-loop mode. The studies also only evaluated SCS systems operating at frequencies of

1200 Hz or below.

An assessment of the published literature on SCS to treat DPN provided information on the specific inherent risks for diabetic patients in the delivery and management of SCS therapy. This included 2545 patients across 12 studies which reported safety and adverse events in an identifiable diabetic population. The analysis of the adverse event profile of SCS to treat DPN showed common adverse event rates were within the ranges reported for the general population of SCS patients, with two notable differences: infection and the potential for blood glucose to fluctuate in response to an adverse event. Of note, there were no differences in the rate of infection between diabetic and non-diabetic patients enrolled in the IDE clinical studies of the Evoke System. Additional risks for diabetic patients include, but are not limited to, delayed wound healing, cardiovascular events, dural puncture and subsequent subdural hematoma. In the analysis of the Evoke System safety data for diabetic patients enrolled in the IDE clinical studies, the adverse events rates for these risks were within or lower than the range reported in the literature. These events may be avoided by appropriate patient selection, and/or by the use of appropriate surgical techniques and procedures.

For intractable pain resulting from DPN, patients have few options after medical management as no disease-modifying intervention beyond medications is available to treat DPN. In two randomized clinical trials comparing SCS to treat DPN to standard-of- care, most patients, as shown above, experienced clinically meaningful reduction in pain symptoms, and most did so beyond the primary endpoints of the studies. In a comprehensive review of the available data on the risks associated with the therapy, the risk profile for DPN patients was generally consistent with the overall risk profile for the general population treated with SCS, with the exceptions of infection and glycemic control. However, there has been no data to suggest that there is an increased risk of infection associated with the use of SCS as opposed to other implantable devices for patients with DPN. These risks are mitigated by the addition of language in the labeling for the population of pain patients with DPN, such that these patients can be properly selected and managed, particularly in the perioperative phase. Thus, for patients who are not contraindicated, the clinical data has demonstrated that SCS offers a safe and effective treatment option for chronic, intractable pain associated with 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 the Evoke 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 for the open-loop stimulation mode for frequencies 1200 Hz and below.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Evoke System 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 resulting from DPN, patients have few options after medical management. In two randomized controlled trials comparing SCS to treat DPN to the standard-of-care, most subjects experienced clinically meaningful reduction in pain symptoms, and most did 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. Furthermore, the rate of these risks in diabetic patients with the Evoke System was found to be within, and in most cases, below the range reported in the literature. These patients have relatively few treatment alternatives, and for patients without contraindications, SCS offers an option for the management of chronic, intractable pain in the lower extremities associated with DPN where the benefits outweigh the risks associated with the therapy.

XIV. CDRH DECISION

CDRH issued an approval order on March 20, 2024.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

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