Vivistim® Paired VNS™ System

Implantable Device Manual for Healthcare Professionals

Implantable Pulse Generator: Model 1001

Stimulation Lead: Model 3000

NOTE: This page identifies the parts included in this Healthcare Professional's Manual. The information contained herein is not intended to serve as a substitute for a complete and thorough understanding of the material presented in all of the manuals for the Vivistim® Paired VNS™ System and its component parts, nor does this represent full disclosure of all pertinent information concerning use of this product, potential safety complications, or efficacy outcomes. Copies of all Vivistim® Paired VNS™ System manuals are included with the system for full disclosure; copies are also available from MicroTransponder, Inc.

Released Version 4

PAT. www.microtransponder.com/patents

Rx Only

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1 BRIEF DEVICE DESCRIPTION

The MicroTransponder® Vivistim® Paired VNS™ System (Vivistim® System) is an active implantable medical device that comprises four main components: (1) an Implantable Pulse Generator (IPG), (2) an implantable Lead, (3) Stroke Application & Programming Software (SAPS), and (4) a Wireless Transmitter (WT). The IPG and Lead are the implantable components; the SAPS and WT are the non-implantable components.

The Vivistim® System when used as intended, provides a drug-free way to treat upper extremity motor deficits associated with a stroke by pairing rehabilitation movements with Vagus Nerve Stimulation (VNS). The Lead electrodes are attached to the left vagus nerve in the neck. The Lead is tunneled from the neck to the chest, where it is connected to the IPG, and the IPG is placed subcutaneously (or sub-muscularly) in the pectoral region. The SAPS is delivered to the clinician preloaded onto a commercially available laptop. The SAPS, via the WT, allows the clinician to program the output settings of the IPG (e.g., amplitude, frequency, pulse width) and read the status and history of the IPG. The SAPS also stores the number of stimulations, task performed, and IPG status that occur for each rehabilitation activity for future review by the clinician.

The SAPS and WT also allow the implanted components (the IPG and Lead) to stimulate the vagus nerve while a rehabilitation movement occurs. The therapist initiates the stimulation using a USB push button or mouse click, which synchronizes the stimulation with an appropriate timepoint during rehabilitation movements. When directed by a physician and with appropriate programming to the IPG, the patient can initiate at-home use by swiping a magnet over the IPG implant site. This activates the IPG to deliver stimulation for about 30 minutes while rehabilitation movements are performed. At-home use does not require the use of SAPS or the WT. In addition, the magnet provided to the patient to initiate home therapy also has a safety feature; holding the magnet over the device stops any inadvertent stimulation for as long as it is held over the device. Patients will be trained in both uses of the magnet.

The complete device system (the Vivistim® System), including the IPG, is shown in Figure 1.1.

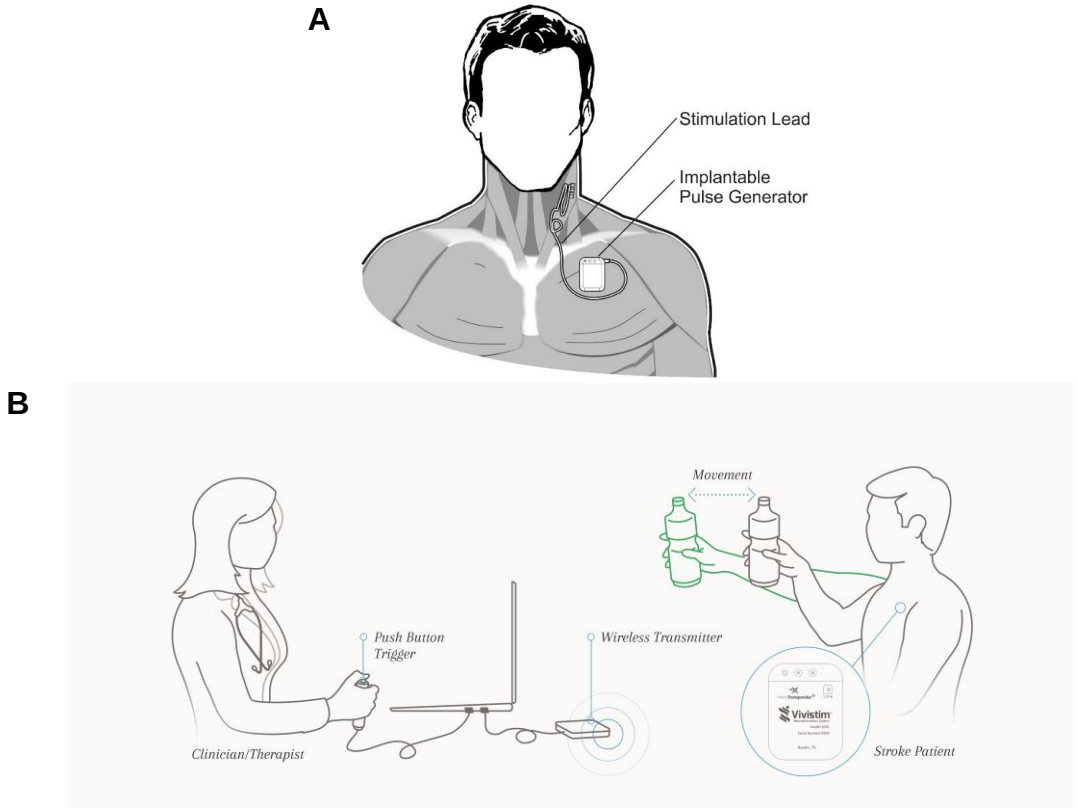

Figure 1.1: (A) Device Placement, (B) In-office Set-up

The IPG and Lead are described in detail throughout this manual. The WT and SAPS are described in further detail in the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals**. However, since an understanding of the complete system is helpful for understanding the implantable components, the WT and SAPS are also summarized further below.

1.1 Wireless Transmitter (WT)

The WT is the bi-directional radio frequency (RF) communication link between SAPS and the implanted IPG. The WT uses the FCC-approved MICS band (~403 MHz) to communicate with the IPG at distances of up to 1 m. The WT has a 2 m cable with a USB connector that plugs into the commercially available laptop. The WT is powered via the USB connection on the laptop and does not require any additional power source, such as its own battery, or additional power connection. The WT is shown in Figure 1.2.

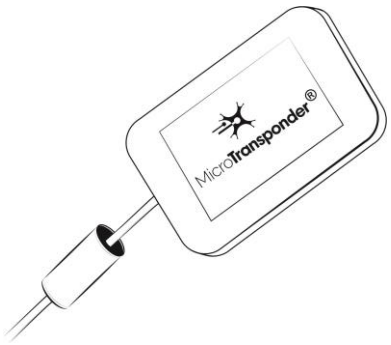

Figure 1.2: Wireless Transmitter

1.2 Stroke Application & Programming Software (SAPS)

The Model 4001 Stroke and Application Software (SAPS) allows the clinician to control the Vivistim® System. Using SAPS, the clinician can set the IPG stimulation parameters, check the status of the IPG battery level, check the Lead impedance, and record the rehabilitation task information. The SAPS also stores the therapy session history for review at a later time. The software is delivered to the clinician pre-installed on a commercially available laptop.

1.3 Symbols and Definitions

This manual and accompanying implantable device labeling use these symbols and definitions. Refer to the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals** for symbols relating to the non-implantable components of the Vivistim® System.

⚠	**Caution, pay special attention to the information following the symbol**
1.27-Bi	**MicroTransponder 1.27-Bi Connector**
	Constant Current Output
	Cuff Size
	Date of Manufacture
	Do Not Resterilize
	Do Not Re-use
	Do Not Use if Package is Damaged
EC REP	**Authorized Representative in the European Union**
STERILE EO	**Sterilized Using Ethylene Oxide**
	Consult Instructions for Use

	**Maximum Implant Depth**
	**Open Here**
	**Open Here**
	**Lead Length**
	**Batch Code**
	**Manufacturer**
	**MR Conditional**
	**Serial Number**
	Temperature Limitation (Storage and Transport)
	Use By Date
	**For Prescription use only**
Rx only	**For Prescription use only**

2 INTENDED USE / INDICATION

The MicroTransponder® Vivistim® Paired VNS™ System is intended to be used to stimulate the vagus nerve during rehabilitation therapy in order to reduce upper extremity motor deficits and improve motor function in chronic ischemic stroke patients with moderate to severe arm impairment.

3 CONTRAINDICATIONS

- **Vagotomy**—The Vivistim® System cannot be used in patients after a bilateral or left cervical vagotomy.

4 WARNINGS

Clinicians should inform patients about all potential risks and adverse events discussed in this manual and the other system manuals.

- **Use**—The Vivistim® System should only be prescribed and monitored by clinicians who have specific training and expertise in the management of stroke and the use of this device. The system should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device. The IPG, Lead, WT, and SAPS should only be used as part of MicroTransponder's Vivistim® System.
- **Not curative**—Clinicians should warn patients that the Vivistim® System has not been determined to be a cure for upper extremity motor deficits associated with ischemic stroke. Patients should be counseled to understand that individual results will likely vary. Beneficial results might not become evident for months or may never occur.
- **Unapproved uses**—The safety and efficacy of the Vivistim® System have not been established for uses outside the **Intended Use / Indication** section of this manual, including, but not limited to, patients with:
  - Acute suicidal thinking or behavior

- History of schizophrenia, schizoaffective disorder, or delusional disorders
- History of rapid cycling bipolar disorder
- History of previous therapeutic brain surgery or CNS injury
- Progressive neurological diseases other than stroke
- Cardiac arrhythmias or other abnormalities
- History of dysautonomias
- History of respiratory diseases or disorders, including dyspnea and asthma
- History of ulcers (gastric, duodenal, or other)
- History of vasovagal syncope
- Only one vagus nerve
- Other concurrent forms of brain stimulation
- Pre-existing hoarseness

- **Diathermy**—Do not use shortwave diathermy, microwave diathermy, or therapeutic ultrasound diathermy (thereafter referred to as diathermy) on patients implanted with a Vivistim® System. Diagnostic ultrasound is not included in this warning.

  Energy delivered by diathermy may be concentrated into or reflected by implanted products such as the Vivistim® System. This concentration or reflection of energy may cause heating.

  Heating of the Vivistim® System resulting from diathermy could cause temporary or permanent nerve, tissue, or vascular damage. This damage may result in pain or discomfort, loss of vocal cord function, or even possibly death if there is damage to blood vessels.

  Because diathermy can concentrate or reflect its energy off any size implanted object, the hazard of heating is possible when any portion of the Vivistim® System remains implanted, including just a small portion of the Lead or electrode. Injury or damage can occur during diathermy treatment whether the Vivistim® System is turned on or off.

  Diathermy is further prohibited because it may also damage the Vivistim® System components resulting in loss of therapy, requiring additional surgery for system explantation and replacement. All risks associated with surgery or loss of therapy would then be applicable.

- Advise patients to inform all healthcare professionals that they should not be exposed to diathermy treatment.
- **Worsening depression/suicidality**—Patients being treated with adjunctive Paired VNS™ who have moderate or severe depression should be observed closely for clinical worsening and suicidality, especially at the time of Paired VNS™ stimulation parameter changes or drug or drug dose changes, including either increases or decreases in the stimulation parameters or concomitant treatments. Consideration should be given to changing the therapeutic regimen of Paired VNS™ or concomitant treatments, including possibly discontinuing Paired VNS™ or the concomitant therapy, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.
- **Dysfunctional cardiac conduction systems**—The safety and effectiveness of the Vivistim® System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Evaluation by a cardiologist is recommended if the family history, patient history, or electrocardiogram suggests an abnormal cardiac conduction pathway. Serum electrolytes, magnesium, and calcium should be documented before implantation. Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

  It is important to follow recommended implantation procedures and intraoperative product testing described in the **Recommendations for Implantation** section of this manual. During intraoperative Lead Impedance Diagnostics of other vagus nerve stimulation systems, infrequent incidents of bradycardia and/or asystole can occur. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a Lead Impedance Check or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Additionally, postoperative bradycardia or asystole has been reported rarely in epilepsy and depression patients receiving VNS Therapy® (although none have been reported as of June 8, 2020, with Paired VNS™). If a patient has experienced asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate, the patient should be placed on a cardiac monitor.

The safety of this therapy has not been systematically established for patients experiencing bradycardia or asystole during Paired VNS™.

- **Swallowing difficulties**—Difficulty swallowing (dysphagia) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties are at greater risk for aspiration. Appropriate aspiration precautions should be taken for such patients.
- **Dyspnea or shortness of breath**—Dyspnea (shortness of breath) has not been reported with Paired VNS™ but has been reported with VNS Therapy®. Any patient with underlying pulmonary disease or insufficiency, such as chronic obstructive pulmonary disease or asthma, may be at increased risk for dyspnea and should have their respiratory status evaluated prior to implantation and monitored following initiation of stimulation.
- **Obstructive sleep apnea**— Although worsened apnea has not been reported with Paired VNS™, it has been reported with VNS Therapy®. Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or increasing the Train Period may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder. It is recommended that patients being considered for Paired VNS™ who demonstrate signs or symptoms of OSA, or who are at increased risk for developing OSA, should undergo the appropriate evaluation(s) prior to implantation.
- **Device malfunction**—Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage and other associated problems. Patients should be instructed to end the current therapy session and/or use the magnet to stop stimulation if they suspect a malfunction, and then to contact their clinician immediately for further evaluation. Prompt surgical intervention may be required if a malfunction occurs.
- **Magnetic resonance imaging (MRI)**—Reference the **MRI Safety Information** section of this manual.
- **Excessive stimulation**—Excessive stimulation at an excess duty cycle (when “on” time is greater than “off” time) has resulted in degenerative nerve damage in laboratory animals.
- **Device manipulation**—Patients who manipulate the IPG and Lead through the skin (Twiddler’s Syndrome) or who have significant chest tissue causing significant movement of the IPG may damage or disconnect the Lead from the IPG and/or possibly cause damage to the vagus nerve. Patients should be warned against manipulating the IPG and Lead.

  NOTE: *See the* ***Clinician Training / Information*** *section of this manual.*
- **Surgery**—Post surgery, patients may commonly experience pain, swelling, and/or tenderness at the surgery site. Other risks of VNS surgery include bleeding, seroma/hematoma, bruising, permanent numbness or other sensations, vocal cord paralysis (VCP), itching, infection, and allergic response to the implanted materials. A detailed list of expected adverse events is included below.
- **Adjacent Equipment** - Use of this equipment adjacent to or stacked with other equipment should be avoided because it could result in improper operation. If such use is necessary, this equipment and the other equipment should be observed to verify that they are operating normally.
- **Accessories** - Use of accessories, transducers and cables other than those specified or provided by the manufacturer of this equipment could result in increased electromagnetic emissions or decreased electromagnetic immunity of this equipment and result in improper operation.”
- **Medications** - It is possible that some medications may interfere with the mechanism of action of VNS and may therefore impact effectiveness of the therapy. Effectiveness has not been established in patients taking: Scopolamine, Atropine, Biperiden (Trihexyphenidyl and Cycrimine, Benztropine and Procyclidine), Prazosin, Clonidine, Tizanidine, Propranolol, Oxprenolol and Metoprolol, Dextromethorphan, Amantadine and Memantine, Haloperidol, Lorazepam, and Lamotrigine.

5 PRECAUTIONS

Clinicians should inform patients about all potential risks and adverse events discussed in this manual.

5.1 General

- Appropriate training is very important. Prescribing clinicians should be experienced in the management and treatment of stroke and should be familiar with the programming and use of the Vivistim® System.
- Physicians who implant the Vivistim® System should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the MicroTransponder® Vivistim® System.
- Use during pregnancy—The safety and effectiveness of the Vivistim® System have not been established for use during pregnancy. There are no adequate and well-controlled studies of Paired VNS™ in pregnant women.
- The Vivistim® System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The Vivistim® System is indicated for use only in stimulating the left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve. The safety and efficacy of the Vivistim® System have not been established for stimulation of the right vagus nerve or of any other nerve, muscle, or tissue.
- It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the operation.
- Frequent irrigation of both incision sites with generous amounts of bacitracin or equivalent solution should be performed prior to closure. To minimize scarring, these incisions should be closed with cosmetic closure techniques. Also, antibiotics should be administered postoperatively at the discretion of the physician.
- Effects on other medical devices—The Vivistim® System has not been tested with and may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include, but are not limited to, sensing problems and inappropriate device responses.
- Reversal of Lead polarity has been associated with an increased chance of bradycardia in animal studies of unpaired VNS. It is important that the electrodes are attached to the left vagus nerve in the correct orientation.
- The patient can use a neck brace for the first week to help ensure proper Lead stabilization.
- A reset of the device will program the device off (output current = 0.0 mA). When an IPG is reset, its stimulation output is disabled (0.0 mA); however, all settings and device history are preserved. After a successful reset, the IPG stimulation output may be reprogrammed from 0.0 mA as appropriate for the patient to resume operation at their previously programmed settings.

  NOTE: *For more information on diagnostic testing, see the* ***Troubleshooting*** *section.*
- Laryngeal irritation may result from stimulation. Patients who smoke may have an increased risk of laryngeal irritation.
- Potential effects of Lead breaks—Lead fractures may prevent patients from receiving therapy. If a Lead fracture is suspected, perform diagnostic testing to evaluate continuity within the system. If diagnostic testing suggests that a fracture is present, consider turning the Paired VNS™ IPG to 0.0 mA of output current. Continuing stimulation with a fractured Lead may result in dissolution of the conductor material resulting in adverse events, such as pain, inflammation, and vocal cord dysfunction. The benefits and risks of leaving the Paired VNS™ IPG on (actively stimulating) when a Lead fracture is present should be evaluated and monitored by the medical professional treating the patient.
- Some complications may be associated with damage to the vagus nerve.
  - Hoarseness may be caused by device malfunction, nerve constriction, or nerve fatigue. Nerve constriction should be apparent within a few days after implantation and may require explantation of the Lead. Nerve fatigue usually occurs after intense stimulation parameters have been used and might not be associated with any other adverse event. If fatigue is suspected, use of the Vivistim® IPG should be discontinued for several days until hoarseness subsides.

- Persistent hoarseness *not* associated with stimulation suggests possible nerve irritation and should be immediately investigated.
- Trauma to the vagus nerve at the implantation site could result in permanent vocal cord dysfunction or other difficulties due to a damaged nerve.

- Metal objects implanted in the patient near the IPG may interfere with device communication.
- Objects implanted near the IPG or Lead (typically from a separate medical procedure) may migrate and damage the IPG or Lead.

5.2 Sterilization, Storage, and Handling

The IPG and Lead have been sterilized using ethylene oxide (EO) gas and are supplied in a sterile package to permit direct introduction into the operating field. An expiration (or use-before) date is marked on each package. A sterilization process indicator is included in each package. Products labeled as sterile should be used only if the color of the indicator is green or brown for the IPG and green for the Lead.

The implantable portions of the Vivistim® System are nonpyrogenic.

- Store the Vivistim® System between -20°C (-4°F) and 55°C (131°F). Temperatures outside this range can damage components.
- Do not store the Vivistim® System where it is exposed to water or other liquids. Moisture can damage the seal integrity of the package materials.
- Do not implant a device if any of the following has occurred:
  - The device has been dropped, because dropping it could damage the IPG or Lead.
  - The color of the sterility indicator within the inner package is not green or brown for the IPG or green for the Lead, because the device might not be sterile.
  - The outer or inner storage package has been pierced or altered, because this could have rendered it non-sterile.
  - The expiration (use-before) date has expired, because this can adversely affect the device's longevity and sterility.
- Do not ultrasonically clean the IPG or Lead, because doing so may damage the device.
- Do not re-sterilize any Vivistim® System device. Return any opened devices to MicroTransponder.
- The IPG and Lead are single-use-only devices. Do not re-implant an explanted IPG or Lead for any reason, because sterility, functionality, and reliability cannot be ensured and infections may occur.

  NOTE: *See the exterior package label to ascertain the method of sterilization, which is indicated by the EO sterility symbol (see the* ***Symbols and Definitions*** *section of this manual).*

  NOTE: *See the* ***Other Environmental Hazards*** *section of this manual.*

Explanted IPGs and Leads should be returned to MicroTransponder for examination and proper disposal (see **Device Disposal**). Before returning the IPG or Lead, disinfect the device components with Betadine®, Cidex® soak, or other similar disinfectant, and double-seal them in a pouch or other container properly labeled with a biohazard warning.

Do not incinerate the IPG. It contains a sealed chemical battery, and an explosion could result.

5.3 Lead Evaluation and Connection

- Do not use a Lead other than the MicroTransponder® Model 3000 Lead with the Model 1001 IPG, because such use may damage the IPG or injure the patient.
- Do not use the Lead with line-powered equipment (testing equipment or otherwise), because leakage current can injure the patient.
- Do not insert a Lead in the IPG Lead receptacle(s) without first visually verifying that the setscrew(s) is sufficiently retracted to allow insertion. Avoid backing the setscrew(s) out further than needed for Lead insertion.

- To avoid damaging (stripping) the setscrew(s) and/or dislodging the setscrew plug(s), insert the torque wrench into the center of the setscrew plug, keeping the torque wrench perpendicular to the IPG. Slightly rotating the torque wrench during insertion into the setscrew plugs is advised to aid insertion and minimize damage to the plugs.
- Inserting the torque wrench into the septum can aid in relieving a vacuum that may be created during Lead insertion or withdrawal.

5.4 Environmental and Medical Therapy Hazards

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If an IPG ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation.

5.4.1 Hospital and Medical Environments

Vivistim® System operation should always be checked by performing device diagnostic testing (see **Diagnostic Testing**) after any of the medical procedures mentioned in this manual. Additional precautions for these procedures are described below.

- For clear imaging, patients may need to be specially positioned for mammography procedures because of the location of the IPG in the chest. (Most routine diagnostic procedures, such as fluoroscopy and radiography, are not expected to affect system operation.)
- Therapeutic radiation and nuclear imaging may damage the IPG's circuitry, although no testing has been done to date and no definite information on radiation effects is available. Sources of such radiation include therapeutic radiation, brachytherapy, stereotactic radiosurgery, cobalt machines, PET scans, and linear accelerators. The radiation effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage and may not be detectable immediately.
- External defibrillation may damage the IPG. Attempt to minimize current flowing through the IPG and Lead system by following these precautions:
  - Position defibrillation paddles perpendicular to the IPG and Lead system and as far from the IPG as possible.
  - Use the lowest clinically appropriate energy output (watt-seconds).
  - Confirm IPG function after any internal or external defibrillation.
- Use of electrosurgery (electrocautery or RF ablation devices) may damage the IPG. During the VNS implantation procedure, do not use electrosurgical equipment after the IPG has been introduced to the sterile field. When performing other surgical procedures on a patient implanted with a Vivistim® System IPG, attempt to minimize the current flowing through the IPG and Lead system by following these precautions:
  - Position the electrosurgery electrodes as far as possible from the IPG and Lead.
  - Avoid electrode placement that puts the IPG or Lead in the direct path of current flow or within the part of the body being treated.
  - Confirm that the IPG functions as programmed after electrosurgery.

CAUTION: Electrostatic discharge (ESD) discharge precautions should be taken before handling the system. A grounded metal object should be touched before touching the laptop, Wireless Transmitter, and push button.

CAUTION: Electrostatic discharge (ESD) may damage the IPG. Care should be taken when using the torque wrench to avoid touching the metal shaft when the torque wrench is engaged with the setscrew of the IPG. This shaft can serve as a path to conduct electrostatic discharges into the device circuitry.

***CAUTION:** The patient should seek medical advice before entering environments that are protected by a warning notice preventing entry by patients implanted with a cardiac pacemaker or defibrillator.*

- Extracorporeal shockwave lithotripsy may damage the IPG. If therapeutic ultrasound is required, avoid positioning the area of the body where the IPG is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the IPG output to 0.0 mA for the treatment, and then after therapy, reprogram the IPG to the original parameters.
- If the patient receives medical treatment for which electric current is passed through the body (such as from a Transcutaneous Electrical Nerve Stimulation [TENS] unit or Functional Electrical Stimulation [FES]), either the IPG output should be set to 0.0 mA or function of the IPG should be monitored during initial stages of treatment.
- Routine therapeutic ultrasound could damage the IPG and may be inadvertently concentrated by the device, causing harm to the patient.
- Other therapies that utilize electrical or RF energy could damage the IPG and may be inadvertently concentrated by the device, causing harm to the patient. If such therapy is required, avoid delivering the therapy in the vicinity of the IPG or Lead. Program the IPG output to 0.0 mA for the treatment, and then after therapy, reprogram the IPG to the original parameters.
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Magnetic resonance imaging (MRI) Conditional

  Please reference the **MRI Safety Information** section of this manual for questions regarding performing MRI on implanted patients.

5.4.2 Home Occupational Environments

Properly operating microwave ovens, electrical ignition systems, power transmission lines, theft-prevention devices, and metal detectors are not expected to affect the Vivistim® System. Similarly, most routine diagnostic procedures, such as fluoroscopy and radiography, are not expected to affect system operation. However, because of their higher energy levels, sources such as transmitting antennas may interfere with the Vivistim® System. It is suggested that the Vivistim® System be moved away from equipment—typically at least 1.8 m (approximately 6 ft)—that may be causing interference. Passive hand/arm splints have been used safely with the Vivistim® System by patients in the clinical studies.

5.4.3 Cellular Phones

Cellular phones should have no effect on the IPG operation. Unlike an implanted pacemaker or defibrillator, the IPG does not sense physiologic signals.

5.4.4 Pressure Hazards

Entering environments where the pressure may exceed 150 kPa absolute pressure may damage the implanted device. Fifteen meters (approximately 50 ft) of water corresponds roughly to 150 kPa absolute pressure.

5.4.5 Contact Sports

Playing certain contact sports (such as boxing) may damage the implanted Vivistim® System.

5.4.6 Other Environmental Hazards

Strong magnets, hair clippers, vibrators, loudspeaker magnets, Electronic Article Surveillance (EAS) System tag deactivators, and other similar electrical or electro-mechanical devices, which may have a strong static or pulsing magnetic field, can cause accidental closure of the reed switch. When the device is programmed to Magnet Mode, momentary closure of the reed switch can initiate a therapy session for the programmed therapy duration (swiping the magnet over the device). Closure of the reed switch for a prolonged amount of time (~30 seconds) terminates stimulation for as long as the reed switch is closed (holding or taping the magnet over the device for an extended period). Patients should be cautioned to keep such devices away from the IPG, typically at least 15 cm (approximately 6 in) away.


CAUTION: *Do not use the Vivistim® System in an environment where explosive or flammable gases are present.*

CAUTION: *Do not use the Vivistim® System in an environment where the non-implantable components of the system may get wet. These components are not waterproof and should be kept dry except for normal cleaning with a damp cloth.*

CAUTION: *Degradation of the Vivistim® system's ability to communicate during exposure to frequency ranges associated with television broadcasts (~203 MHz) and frequency ranges associated with satellites (~400 MHz), including global positioning system (GPS) signals found in cellphones and other mobile electronic devices, can occur. Programming and pairing with the system should be performed either outside of these environments or with this equipment turned off.*

5.4.7 Programming Software

The IPG can be programmed using SAPS. This software should be used on the provided commercially available laptop, which is dedicated only to programming the Vivistim® System.

5.4.8 Implantable Pulse Generator (IPG) and EMI Effects on Other Devices

The Vivistim® System should be moved—typically at least 1.8 m (approximately 6 ft)—away from equipment with which it may be interfering.

Programming or interrogating the IPG may momentarily interfere with other sensitive electronic equipment nearby. The IPG is not expected to trigger airport metal detectors or theft-protection devices that are further than about 1.8 m (approximately 6 ft).

The IPG may affect the operation of other implanted devices, such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems and inappropriate IPG responses.

The magnet provided for inhibition of the IPG may damage televisions, computer disks, credit cards, and other items affected by strong magnetic fields.

5.4.9 Federal Communications Commission (FCC) Compliance

This equipment has been tested and found to comply with the limits for a Class B digital device, pursuant to Part 15 of the FCC Rules. These limits are designed to provide reasonable protection against harmful interference in a residential installation. This equipment generates, uses, and can radiate RF energy and, if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. However, there is no guarantee that interference will not occur in a particular installation. If this equipment does cause harmful interference to radio or television reception, which can be determined by turning the equipment off and on, the user is encouraged to try and correct the interference by one or more of the following measures:

- Reorient or relocate the receiving antenna.
- Increase the separation between the equipment and receiver.
- Connect the equipment to an outlet on a circuit different from that to which the receiver is connected.
- Consult the dealer or an experienced radio/TV technician for help.

Any modifications to the unit, unless expressly approved by MicroTransponder, could void your authority to operate this equipment.

5.4.10 Device Disposal

- Do not incinerate the IPG, because it can explode if subjected to incineration or cremation temperatures.
- Return all explanted IPGs and Leads to MicroTransponder for examination and safe disposal. Please contact MicroTransponder for additional information.
- Do not implant an explanted IPG or Lead in another patient, because sterility, functionality, and reliability cannot be ensured.

6 ADVERSE EFFECTS

Possible adverse effects include, but are not limited to, the following patient-related conditions:

- Allergic and/or rejection response to the implanted materials
- Damage to blood vessels in the vicinity of implant
- Discomfort from the stimulation (such as pain or muscle movement)
- Excessive bleeding associated with implant surgery
- Fibrosis to the extent that it makes it difficult to remove the system without damaging surrounding structures
- Infection at implant site(s)
- Local irritation, seroma, hematoma, erosion, or swelling
- Nerve trauma or damage causing hoarseness, facial palsy, or other effects due to vagus nerve or surrounding nerve damage during implantation
- Other acute symptoms (e.g., coughing, hoarseness, etc., due to stimulation)
- Persistent pain, numbness, or inflammation at the implant site
- Problems with swallowing or hoarseness
- Undesirable change in stimulation over time, possibly due to tissue changes around the electrode(s), Lead or IPG migration, loose electrical connections, or Lead fractures, any of which may require a corrective surgery

7 IPG DETAILED DEVICE DESCRIPTION

7.1 Physical Characteristics

The titanium case of the Model 1001 IPG is hermetically sealed and leak-rate tested. Specially designed feedthroughs using platinum conductors form the electrical connection from the connector blocks to the circuitry through the hermetically sealed enclosure. The Model 1001 IPG accepts the Model 3000 Lead.

7.2 Biological Compatibility

Materials exposed to the subcutaneous environment are biologically compatible. All of these materials have a long history in medical implants and have been found to be tissue compatible.

7.3 Power Source

The power source for the Model 1001 IPG is a Wilson Greatbatch Ltd, Model WG 9086, Li CfX - Lithium / Carbon Monofluoride with an open-circuit voltage of 3.3 V. The battery's maximum available capacity is approximately 2.5 Ah. The voltage in this battery gradually decreases as the battery nears its end of life (EOL).

7.4 X-ray Identification

The IPG can be identified on an x-ray film and will appear as shown in Figure 7.1. The serial number and model number of the IPG are marked on its titanium case but do not appear on the x-ray film. The serial number and model number can be identified by interrogating the IPG with the Programming Software.

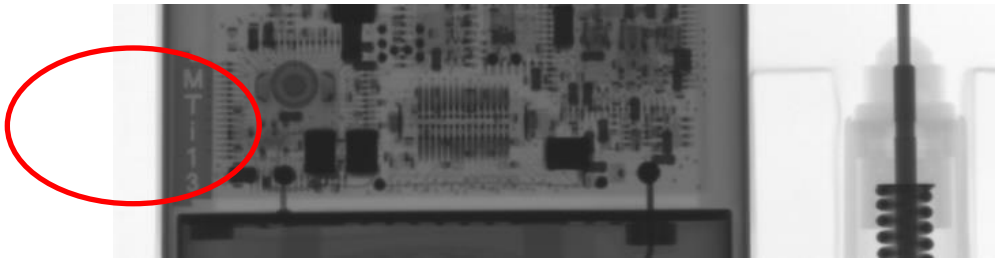


Figure 7.1: X-ray IPG Identification

The radiograph in Figure 7.1 shows a Model 1001 IPG (and the provided torque wrench to the right). The x-ray tag included uses the code MTi13, in which:

- MTi = MicroTransponder® Model 1001
- 13 = The year of manufacture

7.5 IPG Specifications and Product Information

Size	48 mm wide x 62 mm tall x 12 mm thick
Shape	Rectangular with radius ≥ 2 mm and no sharp corners/edges
Weight	<70 g
Power Source	WG 9086, Li CfX - Lithium / Carbon Monofluoride
Housing (Can)	Titanium
Header Material	Epoxy resin

Table 7.1: Characteristics of the Single Use IPG

Parameter	Range / Tolerance
Output Current	0 to 3.5 mA in 0.1 mA steps; (±0.1 mA ≤1 mA, ±10% >1 mA tolerance), with a maximum 12 V
Frequency	1 to 30 Hz, with the following steps (1, 2, 5, 10, 15, 20, 25, 30); ±1% tolerance
Pulse Width	10 µs to 1000 µs with the following steps (10 µs steps from 10 to 100 µs, 25 µs steps from 100 to 500 µs, and 50 µs steps from 500 to 1000 µs); ±2 µs or 1% tolerance, whichever is greater
Duration	0.5 s to 60 s in 1 s steps, starting at 1 s (e.g., 0.5, 1, 2, 3, etc.); ± 1% tolerance
Identification	Factory-only programmed Model Number and Unique Serial Number that can be retrieved via the RF communications, x-ray ID tag (MTi)
Lead Measure	Report the Lead impedance from 250-12,000 Ω with 20% accuracy
Output	Bipolar output; electrically floating can with at least 10 MΩ DC impedance to either + or –
Upgradability	IPG firmware is wirelessly upgradeable

Table 7.2: IPG Electrical Characteristics

NOTE: *See the* ***MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals*** *for more information on the WT and SAPS.*

NOTE: *Latex is not included in any component of the Vivistim® System.*

8 LEAD DETAILED DEVICE DESCRIPTION

8.1 Lead Specifications and Product Information

The Lead delivers the electrical signal from the IPG to the vagus nerve, is insulated with silicone, and is bifurcated at the nerve end to provide bipolar stimulation. It has 2 helical electrodes (nerve cuffs) and an anchor tether, which are coiled around the left vagus nerve. The connector end of the Lead is tunneled subcutaneously to the IPG pocket. The Lead is available in multiple cuff sizes (refer to Table 8.1). The Lead length, cuff diameter, and serial number are indicated on the tag inside the connector of the Lead.

The Lead and identification tag are shown below in Figure 8.1. Table 8.1 shows Lead characteristics.

8.2 Biological Compatibility

Materials exposed to the subcutaneous environment are biologically compatible. All of these materials have a long history in medical implants and have been found to be tissue compatible.

Figure 8.1: VNS Lead and Lead Identification Tag

Total Length	43 cm
Outer Material (insulation)	Silicone
Lead Body Diameter	2 mm
Conductor Coil	MP-35N Alloy, quadfilar
Connector – Outer Material	Silicone
Connector – Connector Pin	300 series stainless steel; 1.27 mm diameter
Connector – Connector Ring	300 series stainless steel; 2.67 mm diameter
Resistance (connector pin/ring to each electrode)	100 - 250 Ω
Helical Cuff Material	Silicone
Helical Cuff Conductor Material	Pt/Ir alloy
Helical Cuff Separation	8 mm center to center
Cuff Diameter	2 mm or 3 mm
Tie-downs	Four silicone tie-downs

Table 8.1: Characteristics of VNS Lead

9 DIRECTIONS FOR USE

9.1 Operating Characteristics

9.1.1 Communicating with the Vivistim® System

9.1.1.1 Stroke Application & Programming Software (SAPS)

The IPG can be programmed with the SAPS software.

SAPS is used on a commercially available laptop supplied by MicroTransponder that is dedicated only to programming the Vivistim® System. More information on SAPS can be found in the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals**.

9.1.1.2 Wireless Transmitter (WT)

A WT connected to a compatible laptop running the Programming Software is needed to communicate with the IPG. (See the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals**.)

9.2 Prompts and Messages

After the Programming Software has been initiated, the software screens display prompts and messages to aid in communicating with the IPG.

9.3 Communication

The IPG “listens” for a communication signal from the WT. Communication usually takes less than 2 seconds but may be prolonged or interrupted in the presence of electromagnetic interference (EMI). The IPG listens for and implements interrogations, parameter programming instructions, requests for Lead impedance measurement, or Device History inquiries.

In response, the IPG transmits the appropriate information. Each instance of these programming and interrogation events is captured by the Programming Software in a database.

In addition to the Programming Software and WT combination, a magnet can be used for one-way communication to the IPG by activating a reed switch in the electronic circuitry. The magnet can be used to initiate stimulation by quickly swiping the magnet over the IPG, depending on how the Magnet Mode is configured in SAPS. In addition, the magnet can be used to temporarily inhibit stimulation by placing the magnet over the IPG for at least 30 seconds; reference the **Stimulation Inhibition via Application of Magnet** section of this manual (stimulation is stopped for as long as the magnet is over the device).

9.3.1 Typical Parameters

The IPG is programmed to deliver stimulation by the clinician. The stimulation is initiated through a push button, mouse click, or a momentary magnet swipe over the IPG, in accordance with the programmed settings, for the length of time programmed by the clinician. Typically, settings are 0.8 mA, 30 Hz, 100 µs, 0.5 second ON, and the stimulation does not repeat until the therapist initiates it again (usually every 5 to 10 seconds). Stimulation duty cycles greater than 50% are inhibited.

When in Magnet Mode, stimulation is initiated for a programmed duration (typically 30 minutes, with 0.5 second of stimulation every 10 seconds) with a magnet swipe over the IPG.

9.3.1.1 Stimulation Inhibition via Application of Magnet

A magnet is provided to the patient to temporarily inhibit stimulation if the stimulation is too strong or becomes uncomfortable or if there is some device malfunction while the patient is at home. The clinician will also have a magnet available so that stimulation can be easily inhibited if needed.

To inhibit stimulation the user should place the magnet over the patient’s chest where the IPG is located and hold the device in place for at least 30 seconds. Stimulation is inhibited for as long as the magnet is placed over the IPG. If at home, the patient should contact their physician (neurologist or physical medicine & rehabilitation [PM&R] doctor) or therapist for an immediate appointment so that the device can be further tested.

CAUTION: *In the event stimulation continues once the magnet has been removed from the patient’s chest, the magnet must be placed back over the patient’s chest where the IPG is located to inhibit stimulation. The magnet should be held in place and the patient’s physician contacted for further instruction. Stimulation will be inhibited as long as the magnet is held in place.*

9.3.1.2 IPG Interrogation

The IPG can be interrogated to determine the present settings of the stimulation parameters.

9.3.1.3 Programmable Parameters

A graphic representation of VNS (Figure 9.1) depicts the relationship of the programmable parameters. Each parameter can be independently programmed, thereby offering multiple setting combinations from which the clinician may select optimal stimulation for the patient.

Figure 9.1 shows that the output pulse can be varied both by amplitude (output current) and duration (pulse width). The number of output pulses delivered per second determines the frequency.

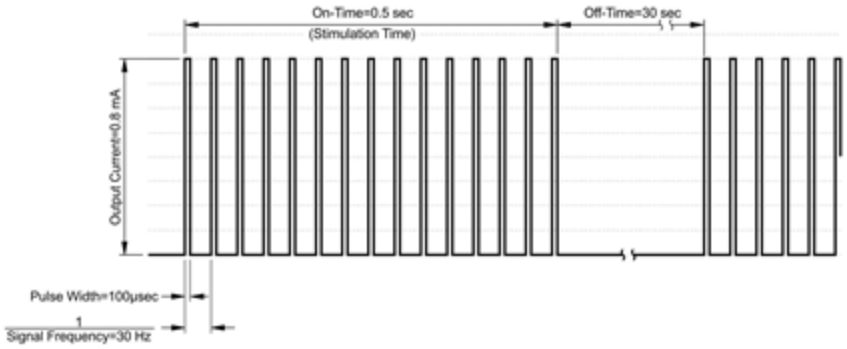


Figure 9.1: Stimulation Waveform

The typical in-clinic VNS session for stroke rehabilitation will be 90 to 120 minutes.

9.3.1.4 Parameter Settings and Battery Life

When selecting a combination of parameter settings for stimulation, the clinician should also consider that some combinations, such as higher output currents and longer “on” times, will decrease battery life faster than others.

9.3.2 Device History

The device history consists of the IPG serial number, model number, patient ID, therapy session tasks, and other information pertinent to diagnostic and programming events. Use the SAPS to access and view device history information.

9.3.3 Check Impedance

Using SAPS, in the ***Patient Information*** portion of the ***Program Implant*** menu, the Lead impedance can be checked by selecting the ***Check*** button. In the top menu bar, selecting the ***Lead Impedance*** button also initiates an impedance measurement. When either the ***Lead Impedance*** button or the ***Check*** button is selected, the IPG delivers a small current to assess Lead impedance. The software displays the measured impedance within the range of 250-12,000 Ω. High Lead Impedance is defined as any value ≥10,000 Ω. Low Lead Impedance is defined as any value <250 Ω.

CAUTION: *Possible causes of High Lead Impedance readings are thought to include: fibrosis between the nerves and the electrode, Lead discontinuity, and Lead disconnection from the IPG.*

CAUTION: *Possible causes of Low Lead Impedance readings are thought to include: short circuit condition within the Lead and a defective IPG.*

9.3.3.1 High Lead Impedance: Possible Implications

High Lead Impedance (warning displayed at ≥10,000 Ω), in the absence of other device-related complications, is an indication that it is difficult for the IPG to deliver the programmed output current and that the battery may therefore not last as long as typical. In conjunction with the patient’s failure to feel stimulation, High Lead Impedance may indicate a Lead wire fracture or other type of electrical discontinuity in the Lead. Patients experiencing High Lead Impedance, no sensation of stimulation, and worsening of upper extremity motor deficits should be further evaluated for possible Lead replacement.

9.3.3.2 Low Lead Impedance: Possible Implications

Low Lead Impedance likely indicates the existence of a short-circuit condition (warning displayed at ≤250 Ω, although an impedance value of >250 Ω does not exclude the possibility of a short-circuit). A sudden decrease in impedance value in combination with device-related complications (e.g., increase in upper extremity motor deficits or painful stimulation; patient perception of feeling erratic, limited, or no stimulation) may also indicate a short-circuit condition in the Lead.

9.3.4 Implantable Pulse Generator (IPG) Battery Longevity

9.3.4.1 Battery Longevity and Programmed Setting Choices

The anticipated longevity of the IPG battery varies, depending on the choice of settings. Higher output currents, frequencies, pulse widths, and duty cycles generally deplete the battery over a shorter period of time than lower settings. Generally, the increase in battery depletion rate is proportional to the increase in the programmed setting.

Other factors, such as the Lead impedance, also affect the anticipated longevity of the IPG battery. The anticipated battery longevity decreases as Lead impedance increases. Although 1000-3000 Ω may be typical Lead impedance at implantation, the impedance may increase to 3000-5000 Ω during the life of the implant.

The approximate battery longevity predicted is greater than 5 years at programmed settings of 1.5 mA in to 3000 Ω load, 50 Hz, 500 µs pulse width, 0.5 second pulse train, and a separation of 15 seconds between pulse trains. Because of the number of possible parameter combinations, it is impractical to provide the projected life for all possible combinations. Increasing settings (output current, pulse width, duty cycle) will decrease battery life. As impedance increases battery life also decreases.

CAUTION: *Undeliverable output currents—Programming the IPG to a higher than typical output current (above 2 mA) may mean that the current cannot be delivered, depending on the patient's specific impedance. Also, higher output currents may disproportionately increase the battery depletion rate and should be avoided if possible.*

CAUTION: *Battery evaluation at cold temperatures—Low storage temperatures may affect the battery status indicators. In such cases, the battery status indicators should be re-evaluated using the Programming Software after the IPG has been at room or body temperature for 30 minutes.*

9.3.4.2 Battery Status Indicators

The Programming Software will display warning messages after an interrogation or programming of the IPG if the battery is nearing its depletion. The first indication is an Elective Replacement Indicator (ERI) flag, which indicates less than 15% of the battery life is left (likely 9 months or less). The final indication is an end of life (EOL) flag, which indicates less than 5% of the battery life is left. It is recommended that IPG replacement start being considered at ERI. Please refer to the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals** for additional information on these indicators.

The predicted duration between the Beginning of Life (BOL) and the EOL flag is a minimum of 5 years, and the predicted duration between the ERI flag and the EOL flag is a minimum of 3 months at programmed settings of 3.5 mA, 30 Hz, 1000 µs pulse width, 0.5 second pulse train, a separation of 10 seconds between pulse trains, and a magnet mode duration of 30 minutes.

9.4 Implantable Pulse Generator (IPG) Removal and Replacement

All Vivistim® System IPGs eventually require surgical replacement as a result of battery depletion. IPG replacement does not, of itself, require Lead replacement unless a Lead discontinuity is suspected. IPG replacement or removal requires dissection to the IPG's pocket, with care being taken not to damage or cut the Lead. Replacement of the IPG typically requires 30 minutes or less; replacement of the entire system typically requires approximately 90 minutes.

9.5 Lead Lifetime, Removal, and Replacement

A Lead requires replacement when a Lead discontinuity is suspected. An increase in clinical signs and symptoms may signal a need for Lead replacement. Events that can shorten the life expectancy of the Lead are as follows:

- Blunt trauma to the neck and/or any area of the body beneath which the Lead is implanted
- Twisting or picking (Twiddler's Syndrome) at either the implanted Lead or the IPG
- Improper surgical implantation of the Vivistim® System, including, but not limited to, providing an inadequate strain-relief loop, placing sutures directly on the Lead body rather than using the tie-downs, and suturing the Lead body to muscle

CAUTION: *Lead replacement or removal—Replacing or removing Leads because of lack of efficacy is a medical judgment that includes the patient's desires and health status and must be carefully weighed against the known and unknown risks of surgery. At present, no known long-term hazards or risks are associated with leaving the Lead implanted, beyond those already mentioned in this multi-part manual. All precautions and contraindications still should be observed (see* ***Environmental and Medical Therapy Hazards****,* ***Troubleshooting****, and* ***Recommendations for Implantation*** *sections of this manual).*

9.6 Signs of End of Life

The most common reason for the absence of stimulation is battery depletion, although there may be other reasons. When end of life (EOL) occurs, the IPG will disable stimulation and no output will be delivered. If the IPG is not explanted or replaced at EOL, the battery voltage will continue to gradually decrease and communication with the IPG may not be possible.

9.7 Replacement Based on Battery Status Indicators

The SAPS battery status indicators provide warnings that an IPG battery should be monitored more frequently, is near EOL, or has reached EOL. Once these warning messages appear, see recommendations in the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals**.

10 TROUBLESHOOTING

10.1 Diagnostic Testing

To assess the proper functioning of the Vivistim® System, the following diagnostic tests may be performed.

- Interrogation of the IPG to verify proper communication
- Impedance measurement of the Lead
- X-ray of the system to visualize Lead fractures or improper insertion of Lead into the header

10.2 Communication Problems

A communication problem can cause an error message during interrogation; checking impedance; programming of task information or VNS parameters; and while performing any other therapy-required communications.

The most common causes of difficulties communicating are connection issues. Verify that the WT connector is correctly inserted into the computer's USB port. Refer to the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals** for further details.

Failure of the IPG and WT to clearly communicate with each other at any time can be attributed to several factors, such as:

- WT not properly connected to laptop
- Programming in the presence of an EMI signal (i.e., OR lights, programming computer, or other medical device systems). This can be difficult or impossible, but problems can usually be resolved by repositioning the patient, the WT, or the EMI source.
- Movement of the patient away from the WT during communication
- Proximity of IPG or WT to a metal table
- Presence of metal barriers between the IPG and WT
- IPG battery at end of life (EOL)
- Defective WT
- Defective laptop
- Defective IPG

Communication problems are often intermittent and are rarely related to the IPG. The surrounding environment is often the cause of these problems.

In the operating room (OR), if communication was possible before the IPG was inserted into the chest pocket, but is not possible with the IPG inside the pocket, verify that the WT is within 1 m of the IPG and the IPG is implanted 5 cm or less from the surface of the skin.

10.2.1 High Lead Impedance

A High Lead Impedance error message can be attributed to several factors:

- No Lead is inserted into the IPG header
- The Lead is not fully inserted into the IPG header
- The setscrews are not properly tightened onto the Lead terminals
- Incorrect placement of the Lead onto the nerve
- Lack of irrigation of the vagus nerve
- Defective Lead
- Defective IPG

A high impedance warning is normal when interrogating an IPG prior to opening the sterile package.

The most common cause of high impedance errors is incorrect connection of the IPG and Lead. Verify that the Lead is fully inserted into the header and the setscrews appear aligned over the connector pin and connector ring. Verify that the setscrews are fully tightened down by tightening them with the provided torque wrench until the screwdriver clicks. Test Lead impedance again. If there are still issues, untighten the setscrews and remove the Lead. Inspect the Lead connector and header bore for foreign material. Verify that there is no damage to the connector seals. Reinsert the Lead into the IPG and tighten setscrews per the instructions in the **Connect the Lead** section. If issues persist, consider replacing the IPG. If issues continue to persist, consider replacing the Lead.

10.2.2 Safe Mode

In the event the IPG reports a Safe Mode condition, the IPG must be reset in order to resume programming or therapy. Refer to the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals** for details on how to perform a reset.

11 SAFETY AND EFFICACY INFORMATION

The safety information presented in this section derives from 3 MicroTransponder studies of Paired VNS™ for stroke using the Vivistim® System. The first feasibility study (MT-St-01) had 20 patients of which 9 were implanted with a modified Vivistim® System (MicroTransponder IPG and non-MicroTransponder lead); the second pilot study (MT-St-02, full MicroTransponder System) had 17 patients of which all were implanted with the Vivistim® System. The third clinical study (MT-St-03) was the pivotal study and included 108 implanted patients. This section will focus primarily on the pivotal study (MT-St-03) and will briefly review the first two studies. For the pivotal study, the intervention included an acute blinded stage consisting of 6 weeks of in-clinic therapy and 90 days of follow-up. After the 90-day follow-up, patients entered the long-term portion of the study. The information provided includes both the acute and long-term portions through the analysis cut-off date.

11.1 Study Explanation

Patients with moderate to severe upper limb deficits at least 4 months after stroke were enrolled in 3 clinical studies. All continuing patients in these studies were randomized to an active VNS group or a Control group that received the same rehabilitation as the active group:

- All 3 studies included a group that received VNS paired with in-clinic rehabilitation movements for approximately 90 minutes 3 times a week for 6 weeks. Each 90-minute rehabilitation session had approximately 300 to 400 movements paired with VNS. This group was the study treatment group.

- Two studies (MT-St-02 and MT-St-03) had a group that received rehabilitation with only a very small amount of VNS (VNS only for the first 5 movements of the 300 to 400 movements during rehabilitation). This group was a Control group. After the acute study, this group crossed over to VNS and received VNS paired with rehabilitation during the long-term portion of the study. The feasibility study (MT-St-01) had a non-implant Control group that received rehabilitation only. This group exited the study after their acute rehabilitation treatment. In all 3 studies, the Control group received intense, task-specific physical therapy that was similar in quality and quantity received by the VNS group. Intense, task-specific physical therapy represents the best currently available treatment option for stroke rehabilitation (Winstein et al, 2016; Teasell et al, 2020).

Therefore, a total of 134 patients (9 VNS patients from Study MT-St-01, 8 VNS patients from Study MT-St-02, 9 Crossover patients from Study MT-St-02, 53 VNS patients from Study MT-St-03, and 55 Control patients from MT-St-03) received VNS. All studies had enrollment and pre-implant assessments prior to surgery. After surgery, all studies had a pre-therapy assessment, 6 weeks of rehabilitation (either with VNS or with rehabilitation only as a Control), and then assessments at 1 and 30 days after rehabilitation ended for both the VNS and Control group patients. Study MT-St-02 and MT-St-03 also had a 90-day assessment for both the VNS and Control group, at which point the Control group crossed over to receive VNS. All implanted patients continued to receive VNS in the long term.

11.2 Demographics

Twenty patients were enrolled in 2013 at a 2-site UK study (MT-St-01); 9 were implanted with the Vivistim® System. Seventeen patients were enrolled in 2015 and 2016 at 4 sites (3 US, 1 UK); all were implanted with the Vivistim® System. One hundred eight patients were enrolled and implanted in 2017 to 2019 at 19 sites (14 US, 5 UK). Gender, age, and basic stroke information are included in Table 11.1.

	Study MT-St-01		**Study MT-St-02**		**Study MT-St-03**	
	Non-implant Control (11)	**VNS (N=9)**	**VNS (N=8)**	**Control VNS (N=9)**	**VNS (N=53)**	**Control VNS (N=55)**
Gender: Male/Female	9/2	7/2	4/4	5/4	34/19	36/19
Race [N (%)]: Caucasian	11 (100%)	9 (100%)	8 (100%)	9 (100%)	42 (79.2%)	42 (76.4%)
Race [N (%)]: Black	0%	0%	0%	0%	9 (17.0%)	9 (16.4%)
Race [N (%)]: Indian/Other	0%	0%	0%	0%	2 (3.8%)	4 (7.3%)
Age (years) Mean ± SD	60.7 ± 10.7	57.9 ± 17.2	59.5 ± 7.4	60.0 ± 13.5	59.1 ± 10.2	61.1 ± 9.23
Time Since Stroke (M±SD)	1.7 ± 1.3	1.8 ± 1.0	1.5 ± 0.7	1.5 ± 1.3	3.1 ± 2.3	3.3 ± 2.6
FMA-UE Score (M±SD)	45.3 ± 8.4	40.1 ± 9.7	29.5 ± 6.4	36.4 ± 9.4	34.4 ± 8.2	35.7 ± 7.8
Side of Stroke (L/R)	4/7	6/3	1/7	5/4	25/28	26/29

Table 11.1: Baseline Demographics

11.3 Device Performance

The Vivistim® System performed according to its specifications. Very few issues were reported. Most communication issues were resolved by repositioning the WT. No significant IPG or software issues were reported. Two Leads were fractured in study MT-St-03 and had to be replaced shortly after the initial surgery. Most device issues were resolved on the day of the initial report.

11.4 Patient Use and Tolerability

Patients tolerated the device extremely well with no significant events associated with stimulation.

11.5 Adverse Events

11.5.1 Study MT-St-01

No AEs were related to the rehabilitation therapy itself. The adverse device effects were minor with the exception of one that was assigned moderate severity. This participant suffered a left vocal cord palsy and dysphagia from left-

sided phrenic nerve palsy following device implantation which resolved over a 3-week period. The event was confirmed resolved at the 1-year follow-up. One participant reported nausea after a single, long session of VNS and rehabilitation. One participant reported a taste disturbance after surgery (metallic taste) that continued during the first 2 weeks of therapy. One participant reported mild dysphagia in the evening after therapy sessions, noted as a difficulty swallowing a capsule on the evenings after sessions. None of these minor symptoms required changes to the therapy protocol. Six patients had slight hoarseness or neck tingling during stimulation and 3 were not aware of stimulation.

11.5.2 Study Mt-St-02

Of the 17 implanted patients, 15 reported at least 1 adverse event, with similar numbers in each group (7/8 VNS patients, 8/9 Control patients). No new or unexpected events were reported. Most events were unrelated to either surgery or stimulation; where events were at least possibly related, most were thought due to surgery. Most of these were mild and related to surgical pain or swelling.

There were 3 serious adverse events (SAEs) related to surgery: surgical infection, shortness of breath and dysphagia due to intubation, and vocal cord paralysis. These are all expected possible events with this type of implant surgery. Other events reported as at least possibly related to surgery were typical of any kind of surgery (bruising, swelling, pain) or typical for this type of surgery (hoarseness for a week or two after surgery).

The only events possibly related to stimulation included finger swelling, constipation, and heart burn that were reported during the first few days after therapy was initiated. These events were mild and did not pose significant hardship to the patient. One additional subject had a short run of supraventricular tachycardia and premature ventricular contractions (PVCs) during their Holter monitoring; extended monitoring found no ongoing anomalies or evidence of arrhythmias, and the event was not thought to be due to VNS.

11.5.3 Study MT-St-03

Of the 108 implanted patients, 85 (78.7%) reported at least 1 adverse event, with similar numbers in each group (43 VNS patients [81.1%]; 42 Control patients [76.4%]). A total of 334 events were reported (163 VNS, 171 Control).These events were typically mild (242) or moderate (87); only 5 events were severe (3 VNS, 2 Control). No unexpected events were reported.

There was 1 serious adverse event (SAE) due to surgery: a dysphonia (from vocal cord paresis) due to the implant surgery. The dysphonia was reported as resolved without intervention after approximately 5 weeks and was verified as resolved via videoendoscopy a couple of months later. No other SAEs reported were associated with the device therapy or surgery. None of these events were new or unexpected types of events.

Most events resolved within a few weeks of the surgery and therapy initiation. Related events were typical of events reported for VNS in epilepsy and depression and were typically either mild or moderate. A table summarizing adverse events is included below in Table 11.2 (all events reported in more than 5% of patients).

Adverse events reported as at least possibly related to surgery were typical of any kind of surgery (bruising, swelling, pain) or this type of surgery (hoarseness or local throat pain or coughing for a few days after surgery). Events most commonly reported as at least possibly related to stimulation were coughing, hoarseness, throat irritation, and pain.

	VNS (N = 53)	**Control (N = 55)**	**All Patients (N = 108)**
Total Number of AEs	**163**	**171**	**334**
Number (%) of Patients with at Least One AE	**43 (81.1%)**	**42 (76.4%)**	**85 (78.7%)**
Gastrointestinal Disorders			
Vomiting/Vomiting with Other	2 (3.8%)	7 (12.7%)	9 (8.3%)
General Disorders			
Pain	5 (9.4%)	7 (12.7%)	12 (11.1%)
Fatigue	3 (5.7%)	2 (3.6%)	5 (4.6%)
Infections and infestations			
UTI	3 (5.7%)	3 (5.5%)	6 (5.6%)
Injury, Poisoning, and Procedural Complications			

	VNS (N = 53)	Control (N = 55)	All Patients (N = 108)
Bruise, Fall/Bruise	8 (15.1%)	4 (7.3%)	12 (11.1%)
Coughing/Cough, Hoarseness	2 (3.8%)	7 (12.7%)	9 (8.3%)
Hoarseness/Voice Alteration	6 (11.3%)	3 (5.5%)	9 (8.3%)
Local Throat Irritation	3 (5.7%)	3 (5.5%)	6 (5.6%)
Fracture	4 (7.5%)	1 (1.8%)	5 (4.6%)
Musculoskeletal and Connective Tissue Disorders			
Pain	5 (9.4%)	9 (16.4%)	14 (13.0%)
Nervous System Disorders			
Dizziness/Dizziness with Nausea	3 (5.7%)	3 (5.5%)	6 (5.6%)
Psychiatric Disorders			
Low Mood/Worsened Depression	5 (9.4%)	4 (7.3%)	9 (8.3%)
Respiratory, Thoracic, and Mediastinal Disorders			
Nasopharyngitis	2 (3.8%)	4 (7.3%)	6 (5.6%)
Coughing	0 (0.0%)	5 (9.1%)	5 (4.6%)
Shortness of Breath	1 (1.9%)	4 (7.3%)	5 (4.6%)
Skin and Subcutaneous Tissue Disorders			
Rash	3 (5.7%)	0 (0.0%)	3 (2.8%)
Surgical and Medical Procedures			
Pain	12 (22.6%)	12 (21.8%)	24 (22.2%)
Hoarseness/Voice Alteration	5 (9.4%)	3 (5.5%)	8 (7.4%)
Vascular Disorders			
Headache	3 (5.7%)	3 (5.5%)	6 (5.6%)

Note: Patients are counted once per event.

Table 11.2: Incidence of Individual Adverse Events (AEs) reported in > 5% of Patients in Either Treatment Group by SOC and Preferred Term Intent to Treat (ITT) Population

The only events reported in more than 5% of VNS patients were pain due to implant (22.6%), bruise/fall (15.1%), general hoarseness (11.3%), general pain (9.4%), hoarseness after surgery (9.4%), low mood (9.4%), muscle pain (9.4%), fracture (7.5%), headache (5.7%), rash (5.7%), dizziness (5.7%), throat irritation (5.7%), UTI (5.7%), and fatigue (5.7%). For the above events, only fatigue, bruising/falls, general hoarseness, fractures, dizziness, hoarseness after surgery, and rash were reported at numerically higher rates for VNS than Control, but none were statistically higher in the VNS group. Although many events were reported numerically more often in the Control group, none were reported statistically more often. Therefore, events are generally similar between groups, with no indication that VNS negatively impacts adverse events.

Events were also assessed by severity; most events were mild and all except 5 events were either mild or moderate.

11.5.4 Relationship to Surgery or Stimulation

Of the 334 total adverse events reported, 163 were in the VNS group and 171 were in the Control group. Forty-three VNS patients (81%) and 42 Control patients (76%) reported at least 1 AE.

For surgical events it is appropriate to consider the 2 groups combined. For AEs reported as at least possibly, probably, or definitely related to surgery, a total of 45 patients (42%) reported related events (21 VNS, 24 Control). The most common event associated with the surgery was pain (22%; 6 possible, 3 probable, 13 definite); this was the only event reported as related to surgery at more than 5%.

Adverse events reported as at least possibly related to stimulation were even rarer. Twenty-five percent of VNS group patients reported at least 1 device-related AE, while 16% of Control group patients reported one. The most common events in the VNS group at least possibly related were hoarseness (5.7%), nausea (3.8%), local throat irritation (3.8%), and coughing (1.9%). The most common events in the Control group at least possibly related were coughing (11%) and hoarseness (3.6%). No other related events were reported on more than 1 subject in either group.

All of these events are expected, and all are at rates lower than expected based on other commercially available VNS therapies, likely due to the fairly low output current (0.8 mA) and pulse width (100 μs).

11.6 Discontinuation Due to Adverse Events

No patients discontinued solely due to adverse events. One subject who discontinued did report his stimulator being uncomfortable in his chest (thin chest with little fat tissue).

11.6.1 Adverse Events Associated with Rehabilitation

Some adverse events reported were likely due to rehabilitation alone. A review of all adverse events indicated shoulder pain; fatigue; neck, back, or trunk muscle pain; muscle pain on paretic arm; and upper extremity spasm were all likely due to rehabilitation movements. These events were reported during or shortly after in-clinic therapy or home exercises. These events are expected based on typical adverse events associated with rehabilitation.

11.7 Serious Adverse Events (SAEs)

Of the 134 implanted patients from all 3 studies, there were 4 serious adverse events (SAEs) due to surgery: surgical infection, shortness of breath and dysphagia due to intubation, and two vocal cord palsies (VCP). Both the infection and shortness of breath/dysphagia events recovered within a few weeks. One VCP recovered within several weeks without intervention while another improved after a gel injection, although the vocal cord did not fully recover.

There were no deaths or unanticipated adverse device effects reported.

11.8 Safety Summary

VNS Therapy® paired with rehabilitation (Paired VNS™) is a safe treatment with a reasonable risk profile. Most events reported were classified as either mild or moderate. Surgical events typically resolved within 1-2 weeks of the surgery. Vocal cord paralysis, associated with patient hoarseness, is a risk that often resolves within 12 weeks, although resolution may take up to 12-18 months and may never fully resolve. Stimulation was usually not bothersome since the settings are brief and typically low; however, if stimulation is bothersome for the patient, the output current or pulse width can be reduced further.

11.9 Efficacy Information (MT-St-02 & MT-St-03)

11.9.1 Results in First 3 Months

11.9.1.1 MT-St-02

This was a blinded, randomized pilot study to assess the safety and feasibility of using paired VNS with upper limb rehabilitation after chronic stroke (Kimberley et al, 2018). With respect to efficacy, the focus of the analysis was on the change in Upper Extremity Fugl Meyer (FMA-UE) in the blinded acute study from the timepoint right before therapy started (V4) to the day after in-clinic therapy was completed (V5) and to the timepoint 30 days after therapy was completed (V7). At V5, the intent-to-treat (ITT) analysis showed a 7.6 (4.8) change for VNS and 5.3 (3.2) change for Controls. At V7, the FMA-UE change for VNS was 8.0 (4.7) and 5.5 (3.4) for Controls. In addition, in the long-term portion of the study (90 days after therapy was completed) there was a 9.5 (6.5) change in FMA-UE for VNS compared to 3.8 (4.8) change for Controls.

11.9.1.2 MT-St-03

The primary and all 3 secondary endpoint analyses were statistically significant. Values presented are averages ± standard deviation (SD) or percent change.

Change in FMA-UE from Baseline (V4) to 1 Day Post Therapy (V5) – Primary			
Visit	**VNS FMA-UE ± SD (N=53)**	**Control FMA-UE ± SD (N=55)**	**P-value (ANCOVA)**
V4	34.4 ± 8.2	35.7 ± 7.8	
V5	39.4 ± 9.5	38.1 ± 9.0	
Difference V5 to V4	5.0 ± 4.4	2.4 ± 3.8	0.0014
Response at 90 Days Post Therapy (V7) First Secondary Endpoint			
Visit	**VNS (% Response)**	**Control (% Response)**	**P-value (Logistic Regression)**
Response at V7*	25/53 (47.2%)	13/55 (23.6%)	0.0098
Response at V5	20/53 (37.7%)	7/55 (12.7%)	0.0017

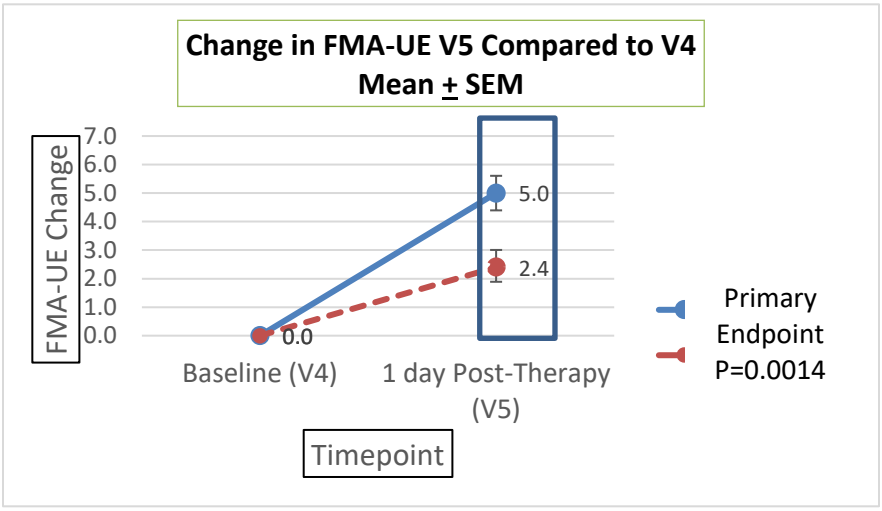
**95% binomial confidence intervals: VNS: (33.30, 61.36); Control: (13.23, 37.02)*

Change in WMFT 90 Days Post Therapy – Second Secondary Endpoint			
Visit	**VNS FMA-UE ± SD (N=53)**	**Control FMA-UE ± SD (N=55)**	**P-value (ANCOVA)**
V4	2.71 ± 0.70	2.83 ± 0.65	
V5	3.04 ± 0.73	2.97 ± 0.68	
V7	3.17 ± 0.77	2.99 ± 0.67	
Difference V7 to V4	0.46 ± 0.40	0.16 ± 0.30	**<0.0001**
Change in FMA-UE 90 Days Post Therapy (V7) - Third Secondary Endpoint			
Visit	**VNS FMA-UE ± SD (N=53)**	**Control FMA-UE ± SD (N=55)**	**P-value (ANCOVA)**
V4	34.4 ± 8.2	35.7 ± 7.8	
V5	39.4 ± 9.5	38.1 ± 9.0	
V7	40.2 ± 10.1	38.6 ± 9.3	
Difference V7 to V4	5.8 ± 6.0	2.8 ± 5.2	**0.0077**

Table 11.3: Primary and Secondary Endpoints

Primary Endpoint

The primary outcome measure for the pivotal MT-St-03 study was the Upper Extremity Fugl-Meyer Assessment (FMA-UE), a stroke-specific measure that assesses motor impairment (Gladstone et al, 2002). The STROKEdge multidisciplinary expert panel recommended using FMA-UE as the primary outcome measure in neurorehabilitation trials for chronic stroke (Bushnell et al, 2015). The recommendations were based on its wide use, excellent psychometric properties and well-established cut-offs for specifying a clinically meaningful response in chronic stroke patients (Page et al, 2012). The FMA-UE is the most widely used and validated measure in upper limb stroke recovery studies (Bushnell et al, 2015; Gladstone et al, 2002).



The primary efficacy endpoint was the change in FMA-UE from V4 (baseline) to V5 (Day 1 post 6 weeks in-clinic therapy). The FMA-UE score increased by 5.0 ± 4.4 points in patients treated with VNS and by 2.4 ± 3.8 points in rehabilitation-only Controls (p=0.0014). The data is shown graphically below.

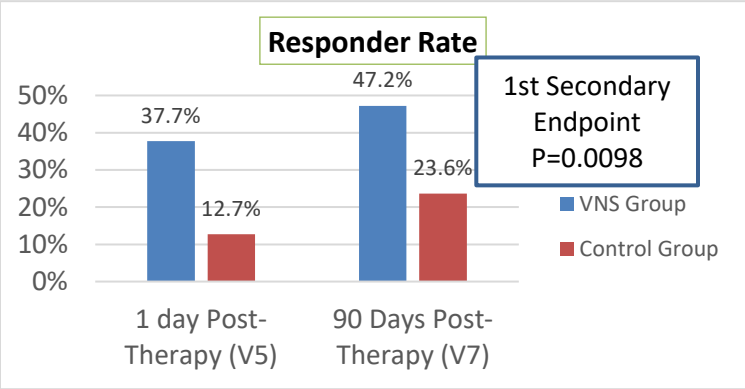
Figure 11.1: Change in FMA-UE – 1 Day Post Therapy (V5) – Primary Endpoint

Secondary Endpoints

The FMA-UE and WMFT were used for assessing secondary efficacy endpoints. The FMA-UE was also recommended for assessing an individual's clinically meaningful improvement (Bushnell et al, 2015; Page et al, 2012). For this study, the clinically meaningful response cut-off was set to ≥ 6-point improvement in FMA-UE score, which is associated with an excellent improvement in overall upper limb function for chronic stroke patients (Page et al, 2012; Kimberley et al, 2019).

The STROKEdge multidisciplinary expert panel also recommended using WMFT as a secondary outcome measure (Bushnell et al, 2015). The WMFT has well-established, psychometric properties for chronic stroke patients including high inter-rater reliability, intra-rater reliability, and responsiveness. The WMFT measures function at the activity domain level (Bushnell et al, 2015).

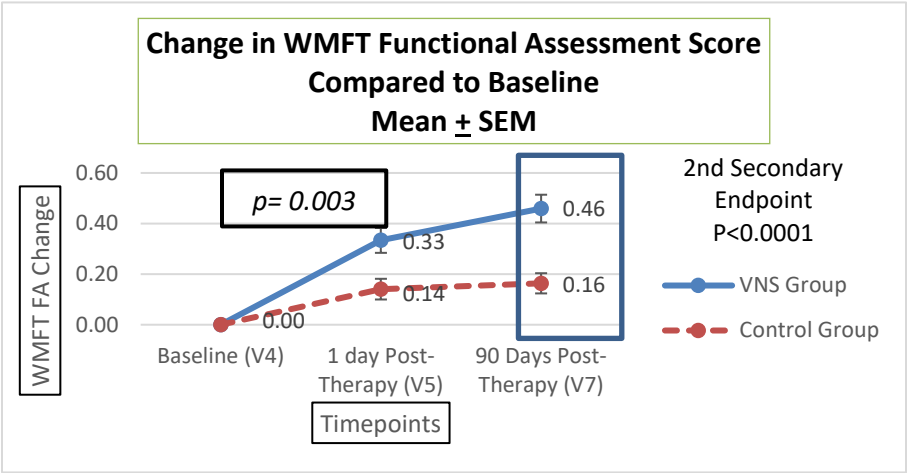
FMA-UE Response at 90 Days Post Therapy (V7) – First Secondary Endpoint



For this study, we defined a clinically meaningful response as a ≥ 6-point improvement in FMA-UE score, (Kimberley et al, 2019) compared to baseline (V4). The response rate on the FMA-UE score 90 days post (V7) 6 weeks of in-clinic therapy was 47.2% in the VNS group compared to 23.6% in Controls (p=0.0098). Although not a primary or secondary measure, responder rates at Day 1 post therapy (V5) are shown for comparison.

Figure 11.2: Response Rate at 90 Days Post Therapy (V7) – First Secondary Endpoint

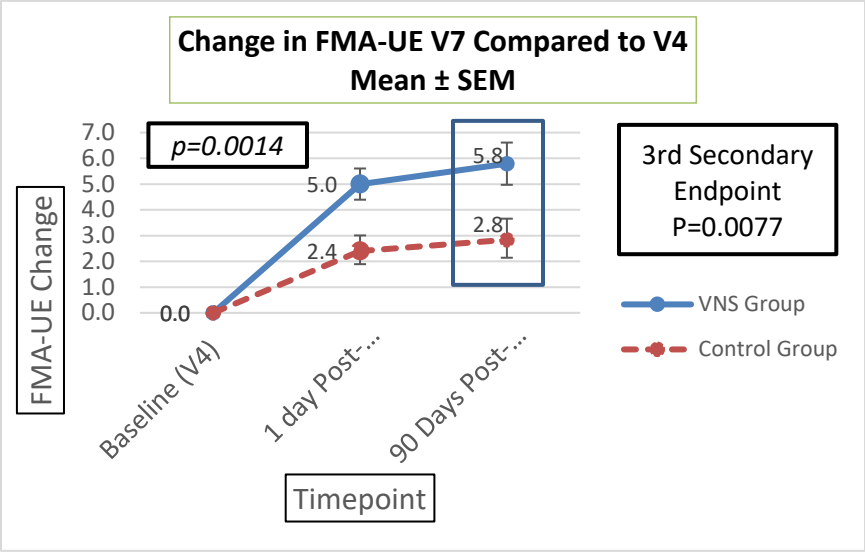
WMFT Change from Baseline to 90 Days Post Therapy (V4 to V7) - Second Secondary Endpoint



The secondary endpoint was a change in WMFT-Functional score from baseline (V4) to 90 days post therapy (V7). At 90 days post therapy (V7), the WMFT-Functional score increased by 0.46 ± 0.40 in the VNS group compared to 0.16 ± 0.30 in Controls (p<0.0001). WMFT change at 1 day post therapy (V5) is shown for comparison. A clinically meaningful group average improvement on the WMFT-Functional score is a > 0.14 change (Lin et al, 2009) and at the 90-day post therapy timepoint, the VNS group had approximately three times this level of change.

Figure 11.3: Change in WMFT 90 Days Post Therapy (V7) – Second Secondary Endpoint

Change in FMA-UE from Baseline to 90 Days Post Therapy (V4 to V7) – Third Secondary Endpoint



This analysis assessed the change from baseline (V4) to 90 days post therapy (V7). At 90 days post therapy (V7), FMA-UE score increased by 5.8 ± 6.0 points in the VNS group and by 2.8 ± 5.2 points in Controls (p=0.0077).

Figure 11.4: Change in FMA-UE 90 Days Post Therapy (V7) – Third Secondary Endpoint

Improvements in the primary as well as all three secondary endpoints were statistically significant. Improvements and changes were seen both immediately after the 6 weeks of therapy (V5), and at the 90-day follow-up (V7).

11.9.2 Long-term Data

11.9.2.1 MT-St-02

Efficacy information is available for 15 of the 17 patients at the 1-year follow-up and 14 patients at the 2-year and 3-year follow-up. The first 2 Control participants discontinued prior to receiving the full crossover VNS—one due to travel concerns and one who was pleased with her benefit and did not want to return for follow-up. The 15 remaining subjects are continuing in the study, however 1 patient missed their 2-year visit and returned for their 3-year visit while another patient returned for her 2-year visit but had her 3-year visit postponed due to Covid-19. Therefore the 15 patients at 1 year had a 9.2-point improvement, and the 14 patients with data had a 10.8-point benefit at 2 years and 14.7-point benefit at 3 years. Control patients responded similarly to VNS patients after crossover to VNS. More than half of subjects responded to therapy and maintained their benefit over time.

11.9.2.2 MT-St-03

Of the 108 patients implanted, long-term data was available at the data cutoff on 66 patients at 6 months of VNS. Analyzing patients from both groups together, patients maintained their benefit—the average FMA-UE score at 6 months for the 66 patients (VNS=36, Control=30) available was 5.9. Although only 42 (VNS=27; Control=15) patients completed the 1-year visit as of the data cutoff date, improvement was maintained, with a 6.8 change in FMA-UE. This indicates that the average improvement for all patients at 1 year is almost 7 points, greater than the conservative 6-point responder cutoff. Benefit is maintained over time.

11.9.3 Tertiary Outcome Measures

Although the primary and secondary efficacy analyses as described above are most important, other efficacy analyses were also supportive. In this study, VNS was favored over Controls with clinically meaningful benefits on a number of other measures. At 90 days post therapy, the VNS group showed a 57% response on function (WMFT-Functional Score) compared to 22% of Controls, with a ≥ 0.4-point change considered a response (Lin et al, 2009). Furthermore, patients in the VNS group showed clinically meaningful benefits for motor activities (MAL) and quality of life measures including activities of daily living (Stroke Impact Scale) and self-care (SS-QOL). After VNS, patients also showed a 2-3 times or greater improvement relative to Controls in motor activities (MAL) and several quality of life domains including activities of daily living (SIS), self-care (SS-QOL), family roles (SS-QOL), and social roles (SS-QOL). Mood (BDI) and overall health (EQ-5D visual analog scale) also showed greater improvements in VNS compared to Control.

11.10 Summary

Improvements in upper extremity motor function were clinically meaningful and were significantly greater with Active VNS compared to Controls receiving the best rehabilitation option currently available. VNS combined with rehabilitation is an effective treatment for improving motor function across multiple domains of impairment, function, and quality of life measures in patients with moderate to severe arm weakness after chronic stroke.

12 ADDITIONAL SAFETY INFORMATION

Except where noted otherwise, the safety information presented in this section derives from the Cyberonics' (LivaNova) studies of epilepsy (E01 to E05) and the pivotal study of VNS for depression (D02). Although from different indications (epilepsy and depression), and using a different device (Cyberonics' VNS Therapy® device), the information from these studies is included here because it is thought to be representative of possible adverse events expected with Paired VNS™ for stroke using the Vivistim® System. The information provided on VNS Therapy® for epilepsy and depression consists of both an acute and a long-term phase showing adverse event and safety data for the respective populations.

The Cyberonics' VNS Therapy® System for refractory epilepsy was implanted in 454 patients in 5 clinical studies involving 611 devices (some patients had IPG replacements). As of August 1996, total VNS Therapy® exposure in these 454 patients was 901 device-years. Individual patient exposure averaged 24 months, with a range of 8 days to 7.4 years.

12.1 Device Performance

The VNS Therapy® System performed according to its specifications. Most device issues were communication difficulties resolved by repositioning the Programming Interface or replacing the Programming Interface batteries. There were several High Lead Impedance issues that occurred requiring Lead replacement. One epilepsy study had an IPG failure that caused nerve damage leading to permanent mild hoarseness.

12.2 Adverse Events Observed in Other VNS Studies

The most common events reported in Cyberonics' (LivaNova) VNS Therapy® product for depression (D-02 Study, VNS group), Table 25 from its Instructions for Use, were: Voice Alteration [hoarseness] (55%), Coughing (24%), Dyspnea (19%), Neck Pain (16%), Dysphagia (13%), Laryngismus (11%), Paresthesia (10%), Pharyngitis (8%), Nausea (7%), and Incision Pain (5%). The most common events reported in Cyberonics' (LivaNova) VNS Therapy® product for epilepsy, Table 55, were: Voice Alteration (60%), Coughing (38%), Pharyngitis (24%), Paresthesia (21%), Dyspnea (21%), Dyspepsia (15%), Nausea (14%), and Laryngismus (5.9%).

Rates from the VNS group in MT-St-03 Paired VNS™ treatment for stroke were comparatively considerably lower: Voice Alteration [hoarseness] (7.5%), Coughing (1.9%), Dyspnea (1.9%), Pain-General (9.4%), Dysphagia (1.9%), Laryngismus (0.0%) [throat irritation was 1.8%], Paresthesia (3.8%), Pharyngitis (3.8%), Nausea (3.8%), and Incision Pain (included within Pain-General). The lower rates are likely a combination of lower stimulation settings and less therapy time (0.8 mA at 100 µs for 0.5 second on movements every 5 to 10 seconds for 2 hours 3 days/week for 6 weeks vs. ~1.5-2.0 mA at 250 or 500 µs for 30 seconds every 5 minutes for 24 hours/day) and reporting differences. Regardless of the reason, there is no evidence for increased adverse effects for the Vivistim® System compared to LivaNova's systems.

The most common adverse events related to surgery were pain, hoarseness or voice alteration, local throat irritation, coughing, and edema. Again, these events are similar to those reported in VNS Therapy® for epilepsy and depression.

12.3 VNS Therapy® and Paired VNS™ Comparison

Adverse event rates from the VNS group in MT-St-03 Paired VNS™ treatment for stroke were considerably lower compared to the LivaNova VNS Therapy® studies of epilepsy and depression. The lower rates are likely a combination of lower stimulation settings and less therapy time (0.8 mA at 100 µs for 0.5 second on movements every 5 to 10 seconds for 2 hours 3 days/week for 6 weeks in MT-St-03 vs. ~1.5-2.0 mA at 250 or 500 µs for 30 seconds every 5 minutes for 24 hours/day) in E-03, E-05, and D-02; there were also likely reporting differences in the different studies. Regardless of the reason, there is no evidence for increased adverse effects for the Vivistim® System compared to LivaNova's systems. It is expected that common adverse events related to surgery, such as pain, hoarseness or voice alteration, local throat irritation, coughing, and edema would be similar for the two systems.

13 BIBLIOGRAPHY

A bibliography of preclinical, clinical, and mechanism of action studies is available from MicroTransponder on request.

14 GUIDELINES FOR PATIENT FOLLOW-UP

During the first few weeks after implantation, the patient should be seen to confirm wound healing and proper Vivistim® System operation. During initial programming, the output current should be programmed to start at nominal parameters (0.0 mA) and then be slowly increased in 0.1 mA increments until the patient feels the stimulation at a comfortable level. The target output current is 0.8 mA, however patients who cannot tolerate this level should have the highest tolerable level below this amount. The typical settings during the clinical study were between 0.5 and 1.0 mA. Patients who are receiving replacement IPGs should also be started at nominal parameters, with 0.1 mA-step increases to allow re-accommodation.

At each patient visit, the IPG should be checked, using the appropriate version of the SAPS. After reprogramming and/or diagnostics testing, data can be printed out and filed. This data can be used for comparison with a patient's own records to evaluate the Vivistim® System, to confirm proper Vivistim® System functioning, and to assess the need for reprogramming. However, all information is also kept in the SAPS database and can be reviewed within the SAPS program.

Vivistim® System treatment should not be uncomfortable, nor should it cause bothersome side effects. Patients should be observed for the first stimulation period or after any stimulation setting adjustment to make certain that they are comfortable with the programmed stimulation.

The subsequent follow-up schedule and the nature of each examination should be determined by the clinician on the basis of patient response to and tolerance of the implant. In all other respects, follow-ups should be performed in accordance with the standard medical practice for patients with upper extremity motor deficits associated with stroke.

In the event intolerable adverse events are reported, clinicians should always try reducing the output current (mA) as a means of eliminating or reducing the severity of an event. Additionally, clinicians should instruct patients or caregivers on the application of the magnet to inhibit stimulation if an adverse event becomes intolerable (see the **Patient Counseling Information** section below). It should be verified that the patient can do this during the first session when stimulation is started; it should also be verified that the patient is given a magnet to take home for this use.

MicroTransponder strongly encourages clinicians to keep all medications stable for the first 3 months of stimulation before attempting to reduce or change a patient's medication.

15 PATIENT COUNSELING INFORMATION

In the unlikely event of uncomfortable adverse events, continuous stimulation, or other malfunction, the patient must be advised to hold or tape the magnet directly over the implanted IPG to prevent additional stimulation. If patients or caregivers find this procedure necessary, they should immediately notify the patient's clinician. The patient should contact their physician or therapist for an immediate appointment so that the device can be further tested.

Patients should also be instructed that they should not manipulate the device or Lead through their skin, as this could damage the device. Pulling on the Lead may move the electrode on the nerve and cause possible nerve damage. Additionally, patients should not pick at their surgical scars.

16 MECHANISM OF ACTION

The following preclinical studies laid the foundation for using VNS paired with rehabilitation for improving upper limb deficits after stroke. VNS paired with movement training significantly enhanced functional recovery of the rat forepaw compared to equivalent rehabilitation training without VNS in models of ischemic and hemorrhagic stroke (Hays et al, 2014; Khodaparast et al, 2016). In several models of ischemic stroke, paired VNS resulted in 2-2.5 times improvement in motor function compared to rehabilitation alone (Khodaparast et al, 2013; Khodaparast et al, 2016; Hays et al, 2014; Hays et al, 2016). The behavioral improvements in motor function after VNS-based rehabilitation were associated with changes in motor cortex connectivity. Paired VNS™ tripled connectivity in corticospinal tracts (CST) controlling the impaired forelimb compared to rehabilitation alone (Meyers et al, 2018). VNS-driven activation of

cholinergic, noradrenergic, and serotonergic neurons, combined with intense, task-specific movement training, reorganized motor cortex and reinforced connectivity in spared motor circuits (Engineer et al, 2019).

17 CLINICIAN TRAINING / INFORMATION

NOTE: *All Vivistim® System programming should be performed by or under the supervision of clinicians familiar with the use and operation of the Programming Software.*

Surgeons implanting the Vivistim® System as well as clinicians supervising use of the Vivistim® System should be thoroughly familiar with all associated training materials, including product labeling for the IPG, Lead, and accessories, including manuals and directions for use.

18 VIVISTIM® SYSTEM DEVICES

18.1 IPG Package Contents

The IPG package contains the following:

- 1 Implantable Pulse Generator (IPG)
- 1 torque wrench
- Documentation

NOTE*: Ensure that at least 1 back-up IPG is available before starting the procedure.*

18.2 Lead Package Contents

The Lead package contains the following:

- 1 Lead
- 4 silicone tie-downs
- Documentation

NOTE: *Ensure that at least 1 back-up Lead is available before starting the procedure.*

18.3 Other Applicable MicroTransponder® Products

- 1 Model 2000 Wireless Transmitter (non-sterile)
- 1 Model 4001 SAPS
- Model 3000 Lead tie-downs

18.4 Applicable Commercial Devices for Use With Vivistim® System IPG

A commercial magnet with a pull force rated at 4.5 kg is sufficient to close the reed switch within the IPG and inhibit stimulation.

18.5 Surgical Materials

The following is a list of additional materials typically used during the Vivistim® System implantation procedure:

- Vessel loops and/or silicone sheet for manipulation of the vagus nerve (suggested but optional)
- Blunt dissection tool (such as blunt forceps, blunt scissors, and/or a tunneler—surgeon’s decision)
- Sterile tube for ease of moving the connector end of the Lead from the neck incision to the chest incision (optional; surgeon may prefer other tools or methods)

18.6 Opening the Sterile Package

Before the package is opened, it should be examined carefully for evidence of damage or compromised sterility. If the outer or inner sterile package has been opened or damaged, MicroTransponder cannot guarantee sterility of the IPG or Lead, and they should not be used. An opened or damaged product should be returned to MicroTransponder.

To open the IPG or Lead sterile package:

1. While holding the outer tray with one hand, grasp the tab on the other side of the package with the other hand and peel back the outer cover.
2. Observing sterile technique, lift out the sterile inner tray.
3. Grasp the inner tray's tab, and carefully peel off the inner cover to expose the contents without dropping them.

NOTE: *The sterile Lead package should only be opened after exposing the vagus nerve.*

NOTE: *Tie-downs could potentially fall out of the Lead package. Carefully remove the Lead to maintain control of the tie-downs.*

⚠ ***CAUTION:*** *Do not use the package if it has been exposed to extreme temperatures or if there is any indication of external damage or damage to the package seal. Instead, return it unopened to MicroTransponder.*

19 RECOMMENDATIONS FOR IMPLANTATION

In general, implantation of the Vivistim® System is similar to accepted practice for implantation of other active implantable devices. The most novel portion of the surgery is the placement of the electrodes and the subcutaneous routing of the Lead connector and body over the clavicle. Although the surgical approach and techniques will vary with the preference of the implanting physician, this part of the manual provides recommendations for implantation, along with a detailed description of the order of placement of the helical electrodes and the anchor tether and other essential steps.

Critical to the long-term success of the implant are proper techniques both for the attachment of the electrodes and the anchor tether to the left vagus nerve and for the provision of adequate strain relief below and above the sternocleidomastoid muscle.

It is recommended that the excess Lead body be coiled and placed loosely in the chest pocket underneath or to the side of the IPG; placement above the generator may cause damage to the Lead body during generator replacement and is therefore not recommended.

Adequate exposure of the vagus nerve (>3 cm) facilitates placement of the electrodes on the nerve. Stretching the nerve or allowing it to dry during implantation may result in temporary swelling of the nerve. Constriction of the nerve or other nerve damage may result in vocal cord dysfunction.

After the electrodes are placed on the nerve, the electrode-nerve interface impedance is tested by connecting the Lead directly to the IPG and performing a Lead Impedance Check.

19.1 Check the Device and Input Patient Data

To ensure proper device communication, using SAPS, check the IPG by communicating with it while still in the sterile package. Refer to the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals** for a detailed explanation.

Using SAPS, program the patient identification into the IPG. See the **MicroTransponder® Vivistim® Paired VNS™ System Non-implantable Device Manual for Healthcare Professionals** for a detailed explanation.

19.2 Procedure Overview

The following overview summarizes the recommended sequence for implanting the Lead:

1. Expose the left carotid sheath and left vagus nerve. Choose the appropriate cuff diameter (2 or 3 mm).

2. Create a pocket in the chest for the IPG.
3. Tunnel the Lead connector and body subcutaneously from the neck to the IPG pocket in the chest.
4. Attach the electrodes and anchor tether to the left vagus nerve.
5. Form the strain relief bend and secure the Lead parallel to the nerve using the provided tie-downs; do not suture around or on the Lead body itself as it may damage it.
6. Form the strain relief loop and secure using the provided tie-downs.
7. Attach the Lead connector to the IPG.
8. Visually verify that the connector pin is fully inserted and the setscrews are over the connector pin and connector ring. Tighten the setscrews.
9. Perform Lead Impedance Check
10. Place the IPG in the chest pocket, with the extra Lead body coiled loosely underneath or to the side of the IPG, not above it. The excess Lead should not be pressed tightly or wrapped against the IPG.
11. Secure the IPG to fascia; do not place sutures directly around or on the Lead.
12. Perform the second Lead Impedance Check.
13. Check the IPG to verify current is 0.0 mA.
14. Irrigate the incision site with bacitracin or other solution.
15. Close the incisions.

19.3 Prepare for Surgery

The surgeon should verify that the IPG and Lead are compatible. MicroTransponder recommends that the patient be given antibiotics preoperatively and that both incision sites be irrigated frequently with generous amounts of bacitracin or equivalent solution prior to closure. (These incisions should be closed with cosmetic closure techniques to minimize scarring.) Also, antibiotics should be administered postoperatively at the discretion of the physician.

CAUTION: *Be careful not to nick or damage the Lead insulation during initial implantation or replacement/revision surgery of either the Lead or IPG. This could cause a leak in the insulation and ultimately allow blood or tissue to pass into the Lead body, which could result in corrosion, damage, and Lead breakage.*

19.4 Lead and Pocket Location

The IPG is usually implanted just below the clavicle in a subcutaneous pocket in the left upper chest. Suggested placement for the Lead is the area of the left vagus nerve half-way between the clavicle and the mastoid process, with the Lead subcutaneously tunneled between the incision site in the neck and the pocket formed in the upper chest (see Figure 19.1). For cosmetic reasons, some surgeons prefer to make incisions within or near Langer's Lines (creases) longitudinal in the neck for nerve access and within the left axilla (armpit) for the IPG pocket. It is recommended that both the Lead body and the IPG be positioned on the left side of the body.

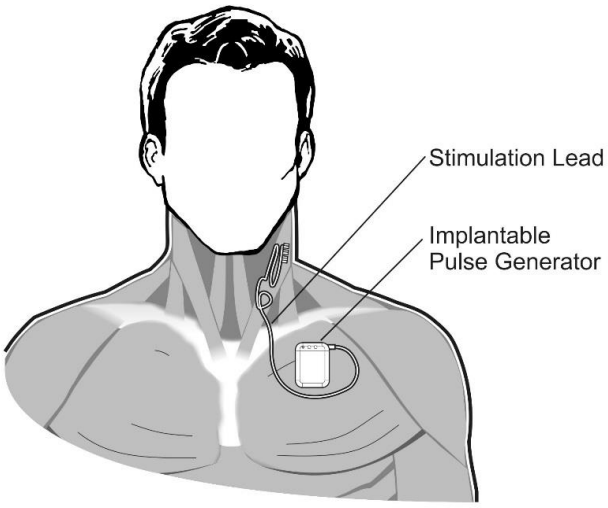


Figure 19.1: Placement of IPG and Lead

19.5 Begin the Procedure

While the specific surgical approach and techniques for implanting the Lead will vary with the surgeon performing the implant, the following detailed instructions are provided for guidance:

1. After administering appropriate anesthesia to the patient, expose the left carotid sheath as it extends along the anterior border of the sternocleidomastoid muscle.
2. Locate and expose *at least 3 cm (1.18 in)* of the left vagus nerve. The recommended stimulation site is a 3-cm section of the vagus nerve, approximately half-way up between the clavicle and the mastoid process, where it is clear of branches (below where the superior and inferior cervical cardiac branches separate from the vagus nerve—see Figure 19.2 and Figure 19.4). The nerve usually lies in a posterior groove between the carotid artery and internal jugular vein. Choose the appropriate cuff diameter (2 or 3 mm) for the nerve size.

   CAUTION: *Extreme care should be taken when isolating the nerve. Manipulation of the nerve should be kept to a minimum. Refrain from squeezing or grabbing the nerve with forceps or other surgical tools as much as possible to prevent nerve damage. Do not stretch or mangle the nerve.*
3. Create a subcutaneous pocket in the chest below the clavicle for the IPG.

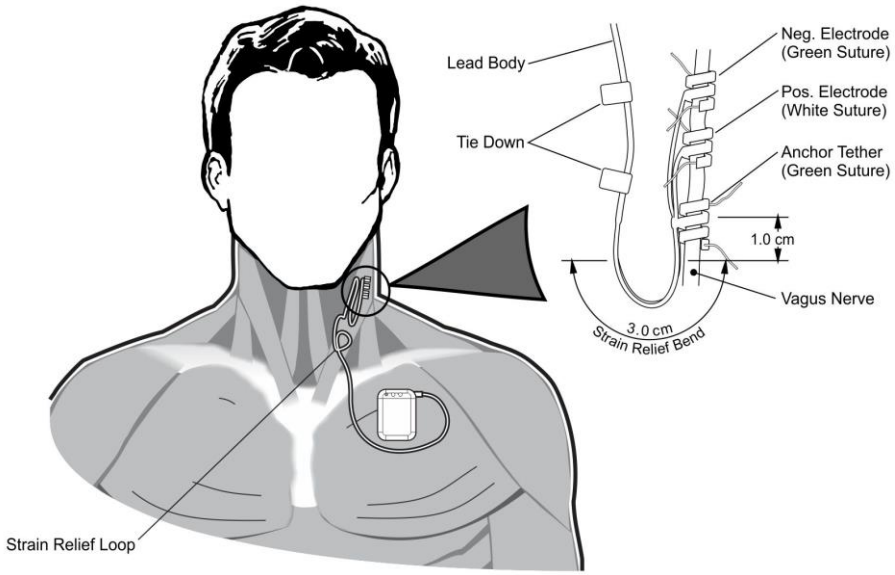


Figure 19.2: Electrode Placement

19.6 Implant the Lead

CAUTION: *Do not expose the Lead to dust or other similar particulates, because its silicone insulation can attract particulate matter.*

CAUTION: *Soaking the Lead in saline or similar solution may cause the insulated portions of the connector pin to swell and become difficult to insert into the IPG.*

19.7 Make a Tunnel and Pass the Lead

The surgeon should use blunt dissection to create a subcutaneous tunnel or pathway from the neck incision to the chest incision. The Lead connector end can then be passed from the neck to chest incision using a sterile tube or similar tool. Although the connector can be passed after the electrode has been placed on the nerve and secured, MicroTransponder recommends that the connector be passed first, in order to avoid the possibility of accidentally putting tension on the electrodes or nerve while passing the Lead connectors.

CAUTION: *To maximize system performance and minimize possible mechanical damage to the nerve or Lead, pay careful attention to Lead routing, Lead stabilization, and electrode placement.*

CAUTION: *Never route the Lead through muscle.*

CAUTION: *Never suture the Lead or Lead body to muscle tissue.*

CAUTION: *Always use the tie-downs to secure the Lead.*

CAUTION: *Do not place sutures directly on the Lead body. Doing so may result in insulation damage or wire failure, causing premature failure of the Lead.*

CAUTION: *If not using a sterile tube or similar tool, care should be exercised when pulling directly on the connector to not damage the connector. Exercise caution to not damage the connector seals if pulling directly on the connector. It is advisable to pull on the connector ring rather than the connector pin, which is more susceptible to bending and damage.*

To pass the tube:

1. With the tube in place between the 2 incisions, carefully insert the Lead connector inside the end of the tube at the neck incision.
2. Carefully pull the tube and Lead connector from the neck incision end until the Lead connector completely exits the chest incision.
3. Remove the Lead connector from the tube, leaving the electrode array at the neck incision site.
4. Discard the tube after use.

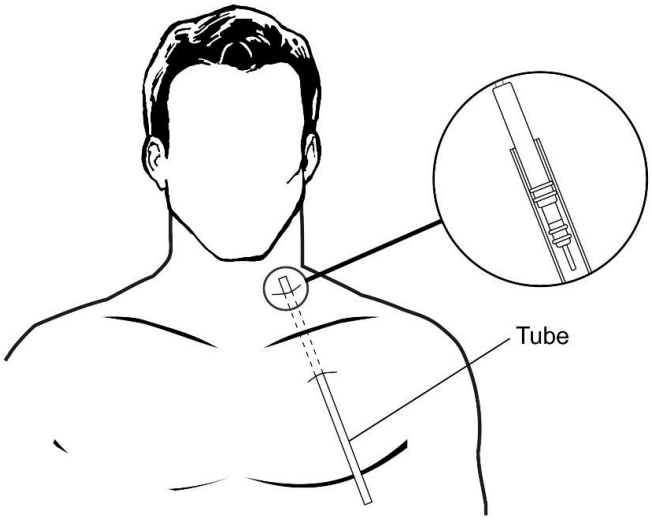


Figure 19.3: Position of Tube and Lead Connector(s)

19.8 Place the Electrodes

It is very important that the surgeon implanting the Vivistim® System be familiar with vagus nerve anatomy, particularly the cardiac branches. The Lead electrodes must not be placed on either the superior or the inferior cervical cardiac branches.

⚠ ***CAUTION:*** *Place the Lead below where the superior and inferior cardiac branches separate from the vagus nerve. Stimulation of either of these 2 branches during the Lead Impedance Check may cause bradycardia and/or asystole. Careful dissection laterally on the vagus nerve should aid the surgeon in determining proper electrode placement. In most but not all patients, the main vagus nerve is the largest of the three nerves. Figure 19.4 shows the correct anatomical placement of the helices.*

⚠ ***CAUTION:*** *When flushing the nerve and neck incision site, be careful not to use a cold solution. Solutions not at body temperature may cause temporary bradycardia or other cardiac effects.*

⚠ ***CAUTION:*** *Excessive manipulation of the vagus nerve during placement of the Lead can result in noticeable post-operative hoarseness. Under most circumstances, this condition will resolve without additional medical intervention within 3-4 weeks, depending on the degree of stress applied to the nerve during surgery. MicroTransponder does not recommend that stimulation treatment be initiated until this condition has resolved, since it could aggravate the condition.*

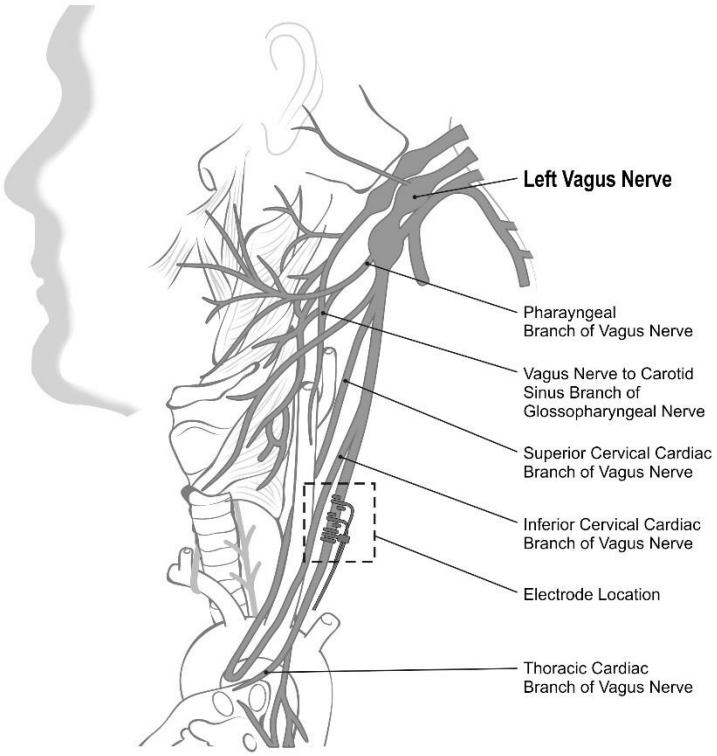


Figure 19.4: Vagus Nerve Anatomy and Placement of the Lead

The helical electrodes and anchor tether are coiled around the nerve, beginning with the electrode that is farthest from the Lead bifurcation (with a green suture embedded in the helical material). This electrode should be nearest the patient's head (further from the IPG in the chest). Next, place the electrode closest to the Lead bifurcation (with white suture; middle spiral) and then place the anchor tether (no electrical connection).

Depending on the surgeon's preference, the helices can alternately be placed by putting the anchor tether on first (furthest from the head; closest to the IPG in the chest), next placing the middle spiral (electrode closest to the Lead bifurcation, with white suture), and then placing the electrode farthest from the Lead bifurcation (with green suture). The polarity of nerve stimulation is controlled by the placement of the electrodes (see Figure 19.5), so it is important to place electrodes correctly, as described. Therefore, the negative electrode (green suture), the electrode at the end of the Lead, furthest from the bifurcation, should be placed cranially. The anchor tether, closest to the bifurcation, should be placed caudally.

The following instructions show placement beginning with the electrode farthest from the Lead bifurcation (green suture).

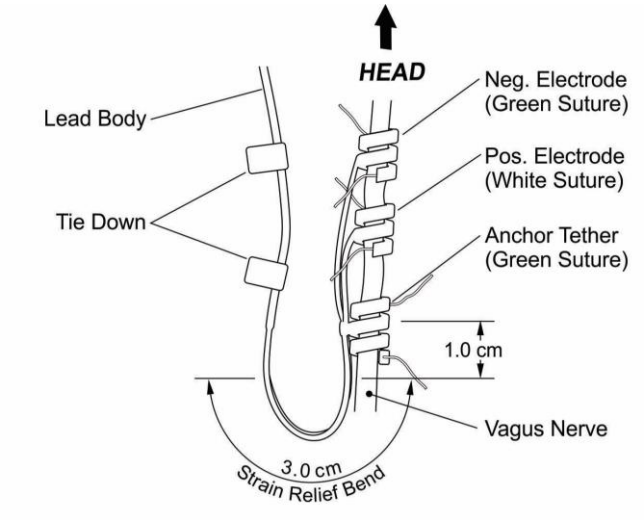


Figure 19.5: Electrode Polarity

The helical electrodes can be placed on the nerve as described below. As an alternative, each helical electrode can be placed underneath the nerve before it is spread. A silicone sheet may be useful to separate the nerve from tissue during the procedure.

1. Place the first helical electrode (negative electrode with the green suture, which will be the closest to the head) in the following manner:

   a. With forceps, gently pull each end of the helix, using the attached sutures to spread the helix (see Figure 19.6).

   ⚠ ***CAUTION:*** *The suture may become dislodged from the helical electrode if product labeling is not followed, i.e., grasping the elastomer and suture separately to manipulate the helical electrode onto the nerve.*

   ⚠ ***CAUTION:*** *The Lead and helical electrodes are very delicate. Take care not to stretch, pinch, or crush the helical electrodes when using forceps. Take care to not over-straighten or stretch the helices when coiling them around the nerve, because doing so may damage the electrode or tether. Use soft rubber vessel loops or equivalent to raise or lift the nerve, if necessary.*

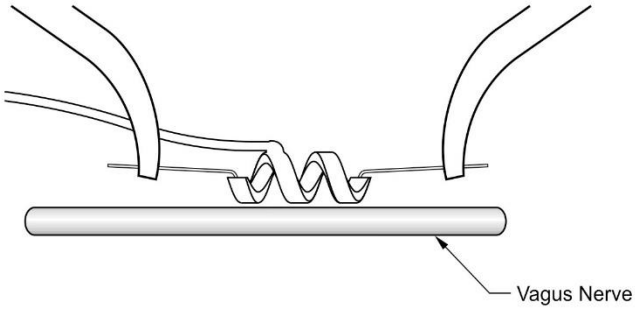


Figure 19.6: Spread the Helical Electrode

   b. Starting with the opened helical electrode spread directly above and parallel to the exposed nerve, turn the helical electrode clockwise at a 45 degree angle to the nerve (see Figure 19.7).

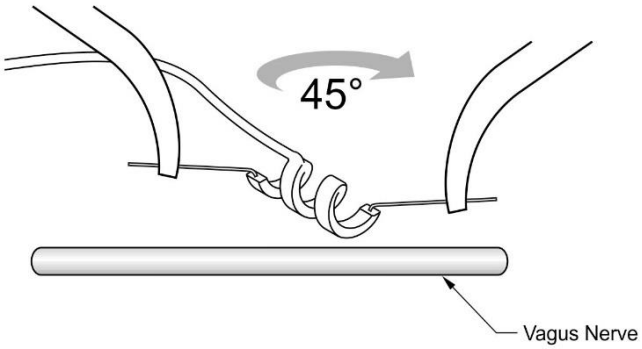


Figure 19.7: Turn the Helical Electrode

c. Place the turn of the helical electrode where the Lead wire connects to the helical electrode (the section with the metal ribbon) onto the nerve (see Figure 19.8).

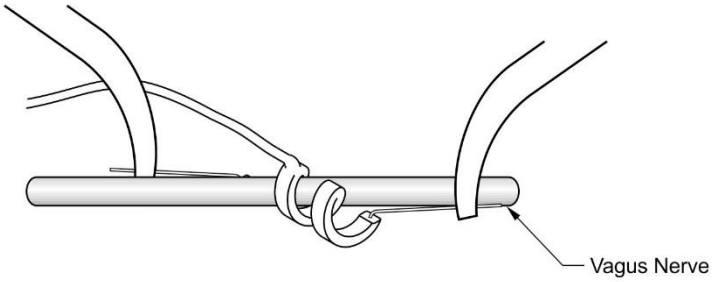


Figure 19.8: Placement of the Turn

d. Pass the *distal* suture portion of the helical electrode under the nerve and back around so that it encircles the nerve (see Figure 19.9 and Figure 19.10).

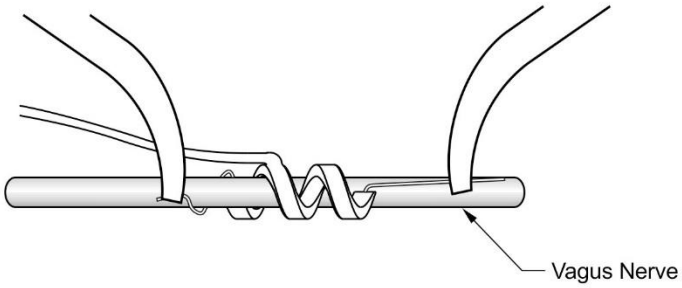


Figure 19.9: Starting to Wrap the Electrode

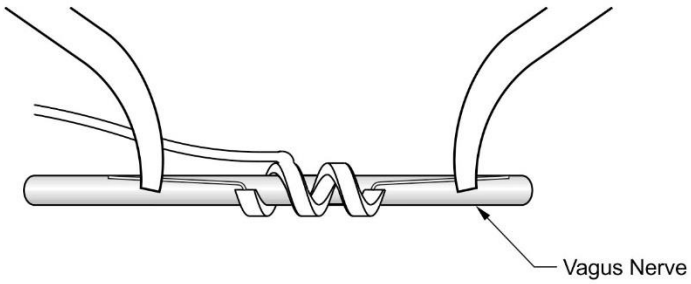


Figure 19.10: Partial Wrap of the Electrode Around Nerve

e. Pass the *proximal* suture portion of the helical electrode under the nerve and back around so that it encircles the nerve (see Figure 19.11).

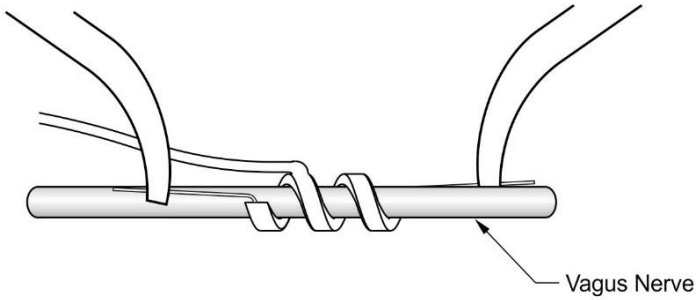


Figure 19.11: Placement of the Proximal Portion of the Helical Electrode

2. Repeat steps 1a-e for the middle helical electrode (the positive electrode with the white suture).
3. Next, place the third helix (this is the anchor tether with green suture but without any electrode portion) around the nerve, following the same general steps as for the other 2 helices.
4. After all 3 helices have been coiled around the nerve, verify that the Lead body exits each helical electrode in the same direction and that the Lead bodies are aligned parallel to each other and to the nerve. The correct placement of the 2 helical electrodes and anchor tether is shown in Figure 19.12.

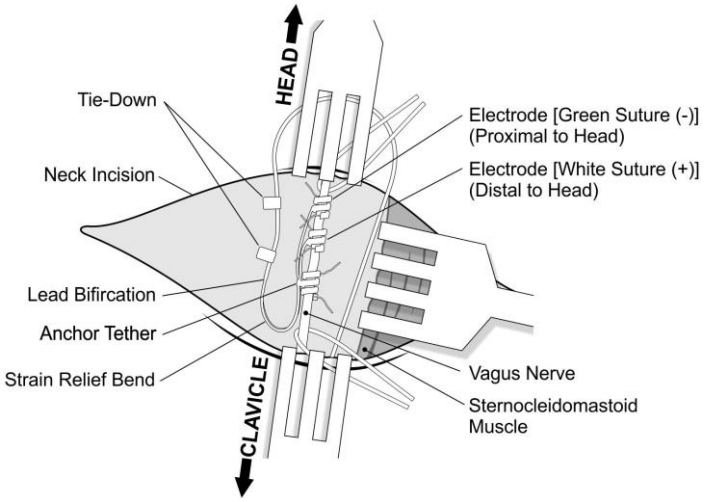


Figure 19.12: Placement of Electrodes and Anchor Tether

CAUTION: *Sutures that are part of the Lead (embedded in the helices of the electrodes and anchor tether) are meant to assist in helical electrode placement around the vagus nerve. These sutures should not be tied to each other or around the nerve, since this may cause nerve damage.*

CAUTION: *Proper techniques for attaching the electrodes and the anchor tether to the left vagus nerve are critical to the long-term success of the implant.*

NOTE*: Provide proper strain relief.*

After attaching the 2 electrodes and the anchor tether, form a strain relief bend and a strain relief loop in the Lead to provide adequate slack and allow for neck movement.

1. To form the strain relief bend (see Figure 19.12 above):
   a. Form the Lead body into a 3-cm (1.18 in) strain relief bend with at least an additional 1 cm (.39 in) of Lead routed parallel to the nerve. The parallel portion can be placed in a pocket formed adjacent to the anchor tether.
   b. Loosely attach the 3-cm strain relief bend to the adjacent fascia with tie-downs. The first tie-down should be positioned laterally to the anchor tether (see Figure 19.13). Four tie-downs are provided in the Lead package.

c. Once the tie-downs are in place route the Lead over the sternocleidomastoid muscle.

CAUTION: *Proper techniques for providing adequate strain relief below and above the sternocleidomastoid muscle are critical to the long-term success of the implant.*

CAUTION: *The Lead insulation and/or Lead conductors may fracture if the recommended strain relief is not provided.*

CAUTION: *The cuffs may dislodge from the nerve or nerve damage may result if adequate strain relief is not provided.*

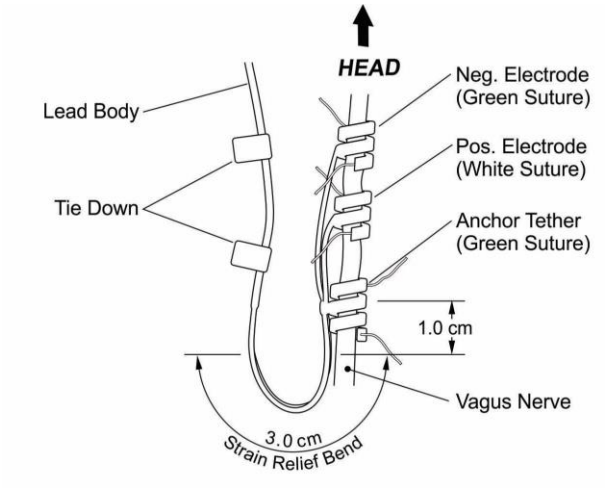


Figure 19.13: Use of Tie-downs in Electrode Placement

2. To form the strain relief loop (see Figure 19.14), do the following above the sternocleidomastoid muscle:
   a. In the neck, form the Lead into a large subcutaneous loop.
   b. Loosely attach it to fascia with a tie-down before routing the Lead over the clavicle. This strain relief loop should be large enough to provide several inches/centimeters of Lead extension when the neck is turned to its maximum stretched positions.

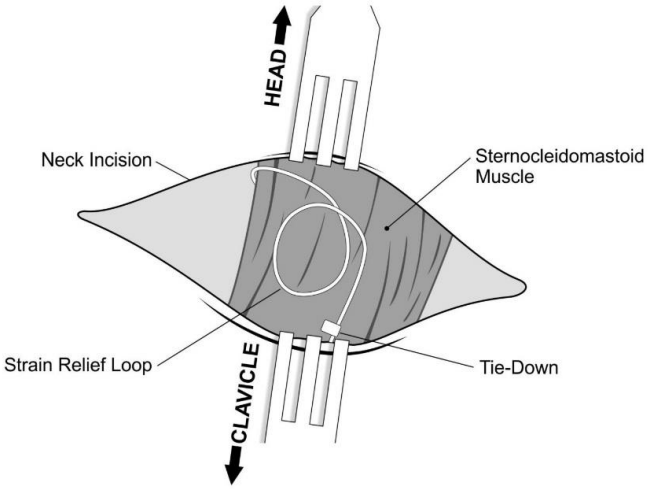


Figure 19.14: Strain Relief Loop

CAUTION: *Leave enough extra Lead on both sides of the clavicle to prevent the tension over the clavicle from damaging the Lead.*

CAUTION: *Placing the sutures directly on the Lead body may result in insulation damage or conductor failure, causing premature failure of the Lead. Use only supplied tie-downs to secure the Lead.*

19.9 Connect the Lead

To connect the Lead directly to the IPG:

1. Look inside the IPG Lead receptacle to verify that no obstruction exists and that the setscrew(s) has been backed out adequately to allow full insertion of the Lead connector pin. Avoid backing the setscrew(s) out further than needed for Lead insertion (see Figure 19.15). The figure is intended to show the contrast between a blocked and a clear receptacle.

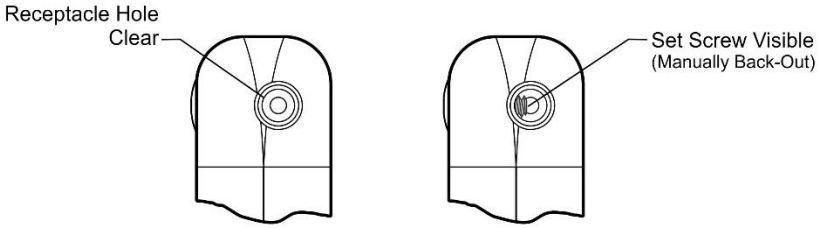


Figure 19.15: IPG Receptacle and Setscrew

CAUTION: *Avoid backing the setscrew out completely when loosening during surgery. Typically no more than 2 counterclockwise turns are required.*

2. Keep the torque wrench perpendicular to the IPG while inserting the wrench through the center of the setscrew plug to vent back pressure accumulated during Lead insertion.

CAUTION: *In the steps below, always push down on the torque wrench while turning it clockwise until it clicks (begins ratcheting), while ensuring that it is fully inserted in the setscrew. Also, the torque wrench must be inserted into the center of the silicone rubber setscrew plug and kept perpendicular to the IPG to avoid stripping the setscrew and/or dislodging the setscrew plug.*

CAUTION: *When using the torque wrench, grasp it by the handle only, as shown in Figure 19.16. Do not grasp any other portion of the torque wrench during use, as this may affect its proper function. Touching the metal shaft while the torque wrench is engaged with the setscrew can conduct an electrostatic discharge into the device circuitry and may damage the IPG.*

CAUTION: *Do not use electrosurgical equipment after the IPG has been introduced to the sterile field. Exposure to this equipment may damage the IPG.*

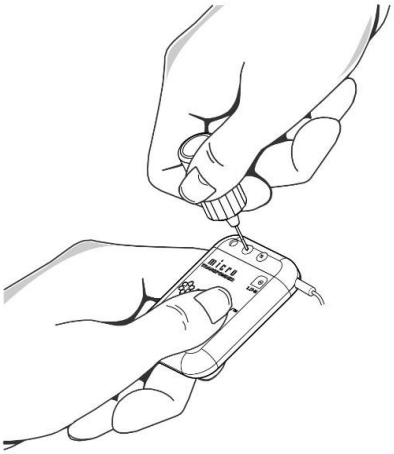


Figure 19.16: Torque Wrench Position

3. Insert the Lead connector pin fully into the IPG header (Figure 19.17, 3 images). To allow escape of the back pressure created by insertion, leave the tip of the torque wrench in the slit in the connector pin setscrew plug.

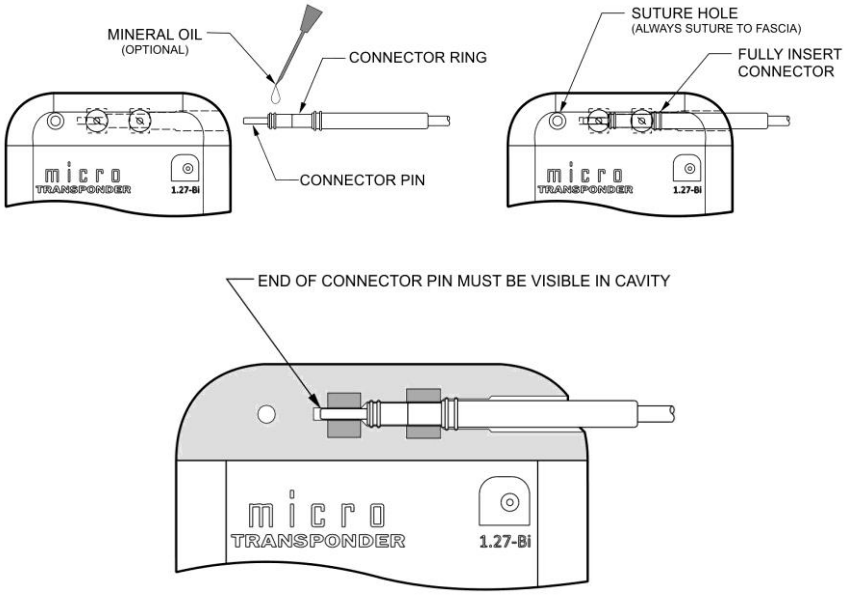


Figure 19.17: Lead Connector Prior to Insertion and Fully Inserted

4. With the torque wrench still inserted through the connector pin setscrew plug, verify that the connector pin is fully inserted. The pin should be visible in the area at the back end of the setscrew connector block. If it is not, one of the setscrews could be blocking the connector pin's pathway and require additional retraction. Withdraw the connector from the IPG header when manipulating the set screws. To retract the setscrews, engage the torque wrench into each setscrew, and turn the wrench counterclockwise slowly until the connector pin can be fully inserted. Avoid backing the setscrews out further than needed for Lead insertion.
5. After verifying that the connector pin has been fully inserted, verify the setscrews are aligned over the connector pin and connector ring. Tighten each setscrew by engaging it with the torque wrench and turning the wrench clockwise until it begins to click. A single click is sufficient for anchoring the Lead. Always push forward on the torque wrench while turning it to ensure that it is fully inserted in the setscrew.
6. Gently grasp and pull on the Lead connector boot (the thick section of the Lead exiting the IPG) to verify that the Lead is properly secured inside the Lead receptacle. Do not pull on the Lead body (thin section) or use excessive pull force, because doing so may cause Lead damage.

⚠ ***CAUTION:*** *It is important to do the following:*

- *Ensure that the receptacle in the IPG is clean and free of obstruction.*
- *Visually inspect that the Lead connector pin is clean.*
- *Carefully insert the Lead connector pin into the receptacle in the IPG without bending the Lead connector. Verify that the Lead connector pin is completely inserted.*
- *Ensure that the torque wrench is engaged into the setscrew before rotating the wrench excessively to avoid damage to the setscrew plug.*
- *Electrical connection to the IPG is not established until the setscrew is completely tightened with the torque wrench. Failure to make a good connection can result in HIGH impedance during a Lead Impedance Check or erratic stimulation at varying intensity due to rapid, unpredictable changes in Lead impedance, which is expected to adversely affect device effectiveness and may have safety consequences such as pain, discomfort, or nerve damage.*

19.10 Test the Vivistim® System

The Lead Impedance Check, which should be conducted first, is performed with the Lead and the IPG connected. Thus, if the Lead Impedance Check is successful, both components are working properly. However, if the Lead

Impedance Check fails, either of the 2 components could be defective, or there may not be a good electrical connection between the IPG and the Lead connector pin or Lead connector ring. First, recheck all connections. If a defective component is suspected in the IPG, disconnect the Lead, connect to another IPG, and then retest the system again using the Lead Impedance Check. If this fails to remedy the issue, disconnect the Lead, replace the Lead, reconnect to the second IPG, and then retest the system again using the Lead Impedance Check.

CAUTION: *During the intraoperative Lead Impedance Check, infrequent incidents of bradycardia and/or asystole may occur. If asystole, severe bradycardia (heart rate <40 bpm), or a clinically significant change in heart rate is encountered during a Lead Impedance Check or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with ACLS.*

Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. If a patient has experienced asystole, severe bradycardia (heart rate <40 bpm), or a clinically significant change in heart rate during a Lead Impedance Check at the time of initial device implantation, the patient should be placed on a cardiac monitor during initiation of stimulation.

The safety of this therapy has not been systematically established for patients experiencing bradycardia or asystole during Vivistim® System implantation.

20 Complete the Implantation Procedure

After the testing has been completed, finish the implantation procedure.

1. Place the IPG in the chest pocket, coiling the remaining slack of the Lead loosely underneath or to the side of the IPG, not above it. The excess Lead should not be pressed tightly against or wrapped around the IPG.
2. Secure the IPG by placing a suture through the suture hole and attaching it to fascia (not muscle).
3. Perform a second Lead Impedance Check.
4. Interrogate the IPG to verify the output is 0.0 mA.

   CAUTION: *Do not program the IPG to ON (greater than 0.0 mA) and initiate a therapy session for at least 1 day after initial or replacement implantation. Failure to observe this precaution may result in patient discomfort or adverse events.*
5. Irrigation of both incision sites with generous amounts of bacitracin or equivalent solution is recommended prior to closure.
6. Close the surgical incisions. Use cosmetic closure techniques to minimize scarring.
7. Administer antibiotics postoperatively (at the discretion of the physician).

A neck brace can be used by the patient as directed by the clinician to help ensure proper Lead stabilization.

21 Patient Identification

Included with the Vivistim® System is an Implant Warranty and Registration Card that must be completed and a copy returned to MicroTransponder. This information, as required by government agencies, becomes part of the MicroTransponder implant documentation and is used as a permanent record of implant recipient information. Additionally, the patient should be given a magnet, patient manual, and Identification Card that contain information about the Vivistim® System. The patient should be instructed to carry the Identification Card at all times.

22 MRI SAFETY INFORMATION

22.1 Introduction

MR Conditional

The Vivistim® System is designated through non-clinical testing as an MR Conditional device that has been demonstrated to present no known hazards when exposed to a specific magnetic resonance (MR) environment that meets specific conditions of use as described in this manual. The Vivistim® System will not be functionally degraded under these conditions of use.

The clinician or radiologist must adhere to the guidelines, cautions, and warnings contained herein in order to perform an MRI on a patient implanted with the Vivistim® System using a 1.5T or 3T MRI closed bore scanner.

This information should be read and understood completely prior to conducting or ordering an MRI examination on a patient with the Vivistim® System. These instructions apply only to the Vivistim® System, and do not apply to other products of any type. If you have any questions, please contact MicroTransponder per the **Information and Support** section of this manual.

22.2 MTI Models and Components Approved for MR Conditional Use

Component	Model/Part Number	Note
Vivistim® Implantable Pulse Generator	1001	Vivistim® System
Lead, 43 cm length, 2 mm cuff diameter	3000	Vivistim® System
Lead, 43 cm length, 3 mm cuff diameter	3000	Vivistim® System

Table 22.1: MTI Models and Components Approved for MR Conditional Use

CAUTION: *No other component of the Vivistim® System is MR Conditional. Do not bring the following Vivistim® System components into the MR room; they are prohibited from MR scanning:*

- *Model 2000 Wireless Transmitter*
- *Model 4001 SAPS software*
- *All non-implantable surgical accessories*

MRI Unsafe: *Do not carry metal (for example magnets, jewelry, etc.) into the MR scanner room. Metal objects can become dangerous flying objects if attracted by the strong magnetic field of the MRI scanner.*

22.3 Risks of MRI With the Vivistim® System

Potential risks of performing MRI outside of the guidance provided in this manual on patients implanted with the Vivistim® System include:

- Lead electrode or IPG can heating, resulting in patient discomfort, tissue damage, or serious injury
- Functional impairment of the IPG, sustained beyond the end of an MRI-scanning session
- Movement, vibration, or rotation of the IPG, resulting in discomfort during MRI scan
- Unintended stimulation during MRI scan
- Image distortion and artifacts of IPG and Lead/electrodes over regions where diagnostic information required

22.4 Contraindications of MRI With the Vivistim® System

The contraindications associated with performing MRI on patients with an implanted Vivistim® System include:

- 3T MRI scans of the C7 to T12 area using a transmit RF body coil require surgical removal of the Vivistim® System unless the whole body averaged SAR is restricted to levels less than or equal to 1.5 W/kg. For details, see the **3T MRI Restricted Zones Overview** section of this manual**.**

- 1.5T MRI scans of the area from the top of the head to L5 using a transmit RF body coil require surgical removal of the Vivistim® System unless the whole body averaged SAR is restricted to levels less than or equal to 0.5 W/kg. For details, see the **1.5T MRI Restricted Zones Overview** section of this manual.
- No part of the implanted Vivistim® System (implantable pulse generator [IPG], Leads, Lead tie-downs) may be within a transmit/receive RF head coil or transmit/receive RF peripheral coil. Scanning of the area where the Vivistim® System is implanted with these types of transmit RF coils is strictly prohibited.
- Do not use open-sided MRI systems or systems operating at higher or lower Tesla values (for example, 0.5, 1.0, 4.0T). The risks of using MRI systems operating at other Tesla values have not been evaluated and could be significant.
- The Model 2000 Wireless Transmitter, Model 4001 SAPS software, all non-implantable surgical accessories, and all off-the-shelf accessories such as the magnet are considered MR Unsafe. These devices may be projectile hazards and should not be allowed into the MRI scan (magnet) room.
- The hazards of scanning patients that are implanted with other medical devices, together with the Vivistim® System, are not known and therefore MR scans on these patients are prohibited until safety has been demonstrated.
- Do not perform an MRI if the patient has a device or device component (Lead, extension, etc.) from a different manufacturer connected to the Vivistim® System IPG. The risks of performing MRI scans with a Vivistim® System IPG connected to a component manufactured by a different company have not been evaluated and could be significant.

22.5 Conditional MRI With the Vivistim® System

MRI examinations of the torso, head, and extremities can be safely conducted in patients with the Vivistim® System when all of the instructions in this manual are strictly followed. Non-clinical testing has shown that the Vivistim® System is MR Conditional when exposed to the MRI environment under the following specific conditions (reference the information found in Table 22.2 and Table 22.3 of this manual):

- A patient with this device can be scanned safely in an MR system meeting the following conditions (Please consult the MR scanner manufacturer for these specifications):
  - Static magnetic field of 1.5 Tesla (1.5T) or 3 Tesla (3T) only
  - Maximum spatial static magnetic field gradient of 5,000 gauss/cm (50 T/m)
  - Gradient magnetic field having a maximum slew rate of 200 T/m/s and amplitude of 40 mT/m
  - For transmit RF head coils in 1.5T and 3T scanners: whole head averaged SAR for the transmit RF coil must be < 3.2 W/kg (Normal Operating Mode).
    - No part of the implanted Vivistim® System (implantable pulse generator [IPG], Leads, or Lead tie-downs) may be within the transmit RF head coil or transmit RF peripheral coil.
    - The location of the implanted Vivistim® System components shall be confirmed prior to the MR scan to ensure compliance with this condition.
  - For transmit RF body coils in 3T scanners centered in the C7 – T12 area: whole body averaged SAR for the transmit RF body coil must be limited as detailed in the **3T MRI Restricted Zones Overview** section of this manual. Adherence to SAR limitations as detailed in Figure 22.1 is absolutely necessary.
  - For transmit RF body coils in 3T scanners centered outside of the C7 – T12 area: whole body averaged SAR for the transmit RF body coil must be < 2 W/kg (Normal Operating Mode).
  - For transmit RF body coils in 1.5T scanners centered in the area from the top of the head to L5: whole body averaged SAR for the transmit RF body coil must be limited as detailed in the **1.5T MRI Restricted Zones Overview** section of this manual. Adherence to SAR limitations as detailed in Figure 22.2 is absolutely necessary.
  - For transmit RF body coils in 1.5T scanners centered outside of the area from the top of the head to L5: whole body averaged SAR for the transmit RF body coil must be < 2 W/kg (Normal Operating Mode).
- Do not conduct an MRI if the implanted Model 3000 Lead is intact but not connected to the IPG.

- Reference the **Consideration for a Partially Explanted Vivistim® System (Remnant Leads)** section of this manual for MR scans of patients with remnant Leads that are less than 5 cm in length.
- The IPG Stimulation and Magnet Mode must be turned off.
- Limit MR scan time to 15 minutes.

Under these defined scan conditions, MicroTransponder's Vivistim® System is expected to produce a maximum temperature rise of less than 6.0 ºC after 15 minutes of continuous scanning.

CAUTION: *Receive RF Coils - Certain MR system head and peripheral RF coils operate in receive-only mode and require the use of a transmit RF body coil. The use of a head or peripheral receive RF coil does not alter hazards of the transmit RF body coil.*

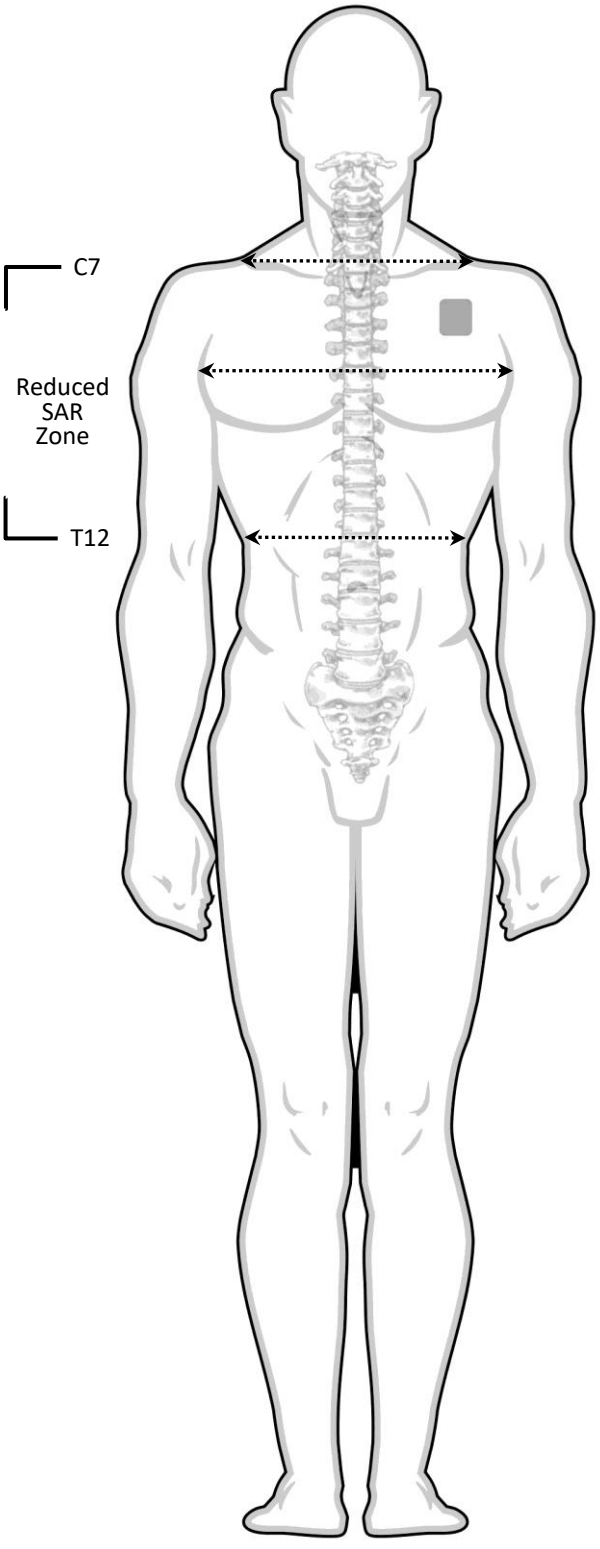
CAUTION: *The RF heating behavior does not scale with static field strength. Devices that do not exhibit detectable heating at one field strength may exhibit high values of localized heating at another field strength.*

In non-clinical testing, the image artifact caused by the Vivistim® System extends approximately 10.4 cm from the IPG and 1.9 cm from the Lead when imaged with a spin-echo pulse sequence in a 3T MRI system and is less in a 1.5T MRI system.

22.6 3T MRI Restricted Zones Overview

Prior to scanning, verify the IPG is programmed to 0.0 mA output and Magnet Mode is programmed OFF.

No part of the Paired VNS™ System can be inside the Transmit RF head coil or Transmit RF peripheral coil.



Zone A: "Normal Operating Mode SAR Limit" zone

When the transmit RF coil is centered in this area, normal operating mode for 3T scans can be performed with the following SAR limitations:

≤ 2 W/kg whole body averaged SAR (Transmit RF body coil)

≤ 3.2 W/kg head average SAR (Transmit RF head coil)

Zone B: "Reduced whole body averaged SAR" zone

Further SAR reductions apply when the transmit RF body coil is centered in this area (C7 – T12):

≤ 1.5 W/kg whole body averaged SAR (Transmit RF body coil)

NOTE: Reduced SAR zone does not apply to transmit RF peripheral coils used on extremities.

Zone A: "Normal Operating Mode SAR Limit" zone

When the transmit RF coil is centered in this area, normal operating mode for 3T scans can be performed with the following SAR limitations:

≤ 2 W/kg whole body averaged SAR (Transmit RF body coil)

Figure 22.1: 3T MRI Restricted Zones Overview

22.7 3T MRI Scan Conditions for the Vivistim® System

MRI Conditions for Use		Zone A: NOM SAR Limit Conditions	Zone B: Reduced SAR Conditions
Scanner Type		Horizontal field, cylindrical closed-bore, clinical system for hydrogen proton imaging	
Scanner Characteristics	**Static magnetic field Strength**	3T	
	Spatial field gradient	< 5,000 G/cm (50.0 T/m)	
	Maximum slew rate	200 T/m/s and amplitude of 40 mT/m	
Scanner Operation	**Operating mode**	Normal Operating Mode (NOM)	Reduced SAR
	Maximum Specific Absorption Rate (SAR)	**Transmit RF head coil**: 3.2W/kg head averaged SAR **Transmit RF peripheral coil:** normal operating mode **Transmit RF body coil:** 2.0 W/kg whole body averaged SAR	**Transmit RF head coils**: N/A ***Transmit RF peripheral coil:** normal operating mode *NOTE: Reduced SAR zone does not apply to transmit RF peripheral coils used on extremities. **Transmit RF body coil:** ≤ 1.5 W/kg whole body averaged SAR
	Transmit RF coil	**Transmit RF head or peripheral coils**: Scan (placement of entire Transmit RF coil) must be outside of C7 - T12. **Transmit RF body Coil:** The iso-center of the scan (center of the MRI bore) must be outside C7 – T12. This may be accomplished by landmarking above C7 or below T12.	**Transmit RF head or peripheral coils**: N/A **Transmit RF body Coil:** The iso-center of the scan (center of the MRI bore) is permitted in this area: C7 – T12. Scans in this zone REQUIRE REDUCED SAR as specified in this column.
	Exposure time	**Transmit RF head or peripheral coils:** No restriction **Transmit RF body coil:** ≤ 15 minutes of active scan time within a 30-minute window	**Transmit RF head or peripheral coils:** N/A **Transmit RF body coil:** ≤ 15 minutes of active scan time within a 30-minute window
	Additional Restriction(s)	**Transmit RF head or peripheral coil:** None **Transmit RF body coil:** Circularly Polarized (CP) mode only (i.e., no shimming)	**Transmit RF head or peripheral coil:** N/A **Transmit RF body coil:** Circularly Polarized (CP) mode only (i.e., no shimming)

Table 22.2: Summary of 3T MR Scan Conditions

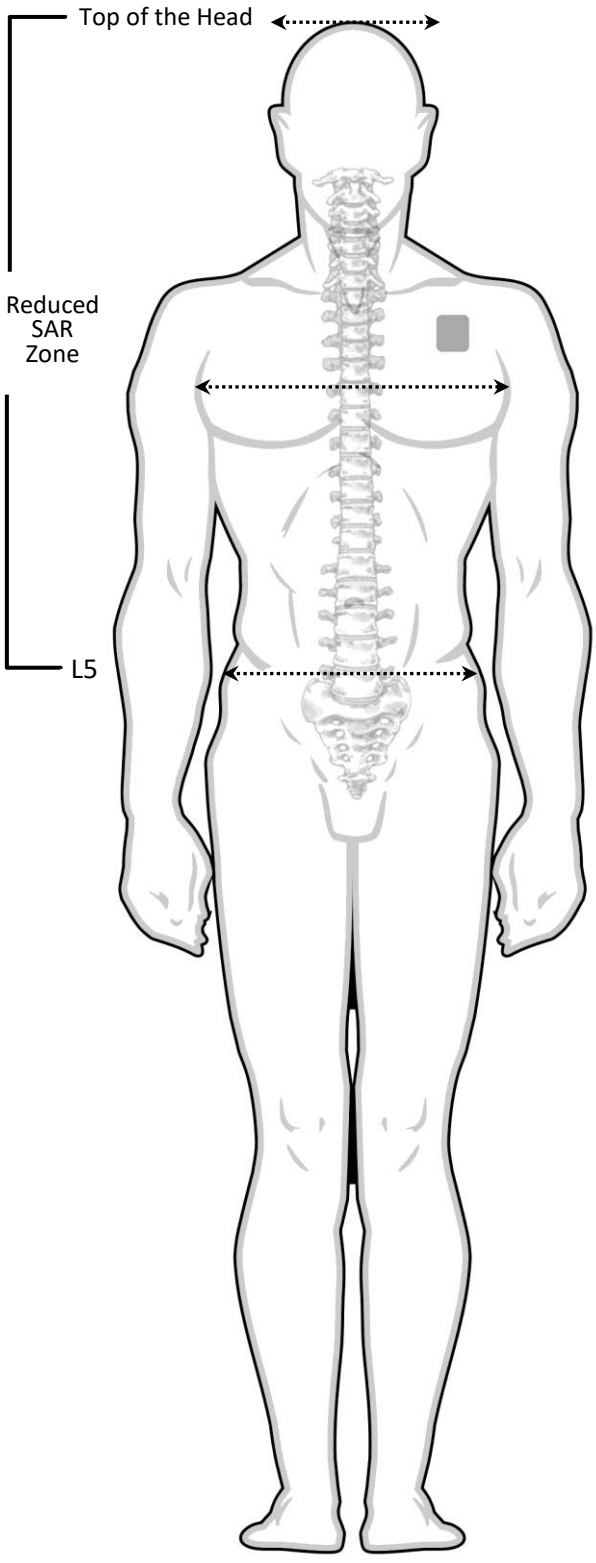
CAUTION: *No part of the Vivistim® System can be inside the Transmit RF head coil or Transmit RF peripheral coil.*

Specific absorption rate (SAR), expressed in watts per kilogram (W/kg), is a measure of RF power deposition in the patient. In MR systems, higher SAR limits lead to greater heating. Typically, SAR values are maximum head averaged when using the transmit RF head coil and whole body averaged when using the transmit RF body coil as reported by the MRI equipment.

22.8 1.5T MRI Restricted Zones Overview

Prior to scanning, verify the IPG is programmed to 0.0 mA output and Magnet Mode is programmed OFF.

No part of the Vivistim® System can be inside the Transmit RF head coil or Transmit RF peripheral coil.



Zone B: "Reduced whole body averaged SAR" zone

Further SAR reductions apply when the transmit RF body coil is centered in this area (Top of Head – L5):

1.5T: ≤ 0.5 W/kg whole body averaged SAR (Transmit RF body coil)

Scans of the head can be performed in normal operating mode for 1.5T scans using the transmit RF head coil with the following SAR limitations:

≤ 3.2 W/kg head average SAR (Transmit RF head coil)

NOTE: Reduced SAR zone does not apply to transmit RF peripheral coils used on extremities.

Zone A: "Normal Operating Mode SAR Limit" zone

When the transmit RF coil is centered in this area, normal operating mode for 1.5T scans can be performed with the following SAR limitations:

≤ 2 W/kg whole body averaged SAR (Transmit RF body coil)

Figure 22.2: 1.5T Restricted Zones Overview

22.9 1.5T MRI Scan Conditions for the Vivistim® System

MRI Conditions for Use		Zone A: NOM SAR Limit Conditions	Zone B: Reduced SAR Conditions
Scanner Type		Horizontal field, cylindrical closed-bore, clinical system for hydrogen proton imaging	
Scanner Characteristics	**Static magnetic field Strength**	1.5T	
	Spatial field gradient	< 5,000 G/cm (50.0 T/m)	
	Maximum slew rate	200 T/m/s and amplitude of 40 mT/m	
Scanner Operation	**Operating mode**	Normal Operating Mode (NOM)	Reduced SAR
	Maximum Specific Absorption Rate (SAR)	**Transmit RF head coil**: N/A **Transmit RF peripheral coil:** normal operating mode **Transmit RF body coil:** 2.0 W/kg whole body averaged SAR	***Transmit RF head coil**: 3.2 W/kg head averaged SAR **–** normal operating mode ***Transmit RF peripheral coil:** normal operating mode *NOTE: Reduced SAR zone does not apply to transmit RF head and peripheral coils used on the head and extremities. **Transmit RF body coil:** ≤ 0.5 W/kg whole body averaged SAR
	Transmit RF coil	**Transmit RF head coil**: N/A **Transmit RF peripheral coil**: Scan (placement of entire coil) must be outside of the Top of Head – L5 area. **Transmit RF body coil:** The iso-center of the scan (center of the MRI bore) must be outside of the Top of Head – L5 area. This may be accomplished by landmarking below L5.	**Transmit RF head coil**: No part of the Vivistim® System can be inside the transmit RF head coil **Transmit RF peripheral coil:** Scan (placement of entire coil) must be outside of the Top of Head – L5 area. **Transmit RF body coil:** The iso-center of the scan (center of the MRI bore) is permitted in this area: Top of Head – L5. Scans in this zone REQUIRE REDUCED SAR as specified in this column.
	Exposure time	**Transmit RF head coil:** N/A **Transmit RF peripheral coil:** No restriction **Transmit RF body coil:** ≤ 15 minutes of active scan time within a 30-minute window	**Transmit RF head coil:** No restriction **Transmit RF peripheral coil:** No restriction **Transmit RF body coil:** ≤ 15 minutes of active scan time within a 30-minute window
	Additional Restriction(s)	**Transmit RF head or peripheral coil:** None **Transmit RF body coil:** Circularly Polarized (CP) mode only (i.e., no shimming)	**Transmit RF head or peripheral coil:** None **Transmit RF body coil:** Circularly Polarized (CP) mode only (i.e., no shimming)

Table 22.3: Summary of 1.5T MR Scan Conditions

Specific absorption rate (SAR), expressed in watts per kilogram (W/kg), is a measure of RF power deposition in the patient. In MR systems, higher SAR limits lead to greater heating. Typically, SAR values are maximum head averaged when using the transmit RF head coil and whole body averaged when using the transmit RF body coil as reported by the MRI equipment.

22.10 1.5T and 3T MRI Scan Scenarios for the Vivistim® System

22.10.1 Brain Scans

Head MRI scans are permissible using 1.5T or 3T scanners using transmit/receive RF head coils. Scan conditions specified in Table 22.2 and Table 22.3 of this manual must be met.

For transmit RF head coils in 1.5T and 3T scanners: whole head averaged SAR must be < 3.2 W/kg (Normal Operating Mode).

- No part of the implanted Vivistim® System (implantable pulse generator [IPG], Leads, or Lead tie-downs) may be within the transmit RF head coil.
- The location of the implanted Vivistim® System components shall be confirmed prior to the MR scan to ensure compliance with this condition.

CAUTION: *Direct exposure of the Vivistim® System to the transmit RF head coil must be avoided. Brain scans that are performed using a transmit/receive RF head coil result in minimal or no exposure of the Vivistim® System to RF energy.*

CAUTION: *Certain MR system head RF coils operate in receive-only mode and require the use of a transmit RF body coil. The use of a receive RF head coil does not alter hazards of the transmit RF body coil.*

22.10.2 Body Scans

Body (torso) scans are permissible using 1.5T or 3T transmit RF body coils. Scan conditions specified in Table 22.2 and Table 22.3 of this manual must be met. Adherence to SAR limitations within these tables and reiterated as detailed in Figure 22.1 and Figure 22.2 is absolutely necessary.

For transmit RF body coils in 3T scanners centered in the C7 – T12 area: whole body averaged SAR must be limited to ≤ 1.5 W/kg.

For transmit RF body coils in 3T scanners centered outside of the C7 – T12 area: whole body averaged SAR must be < 2 W/kg (Normal Operating Mode).

For transmit RF body coils in 1.5T scanners centered in the area from the top of the head to L5: whole body averaged SAR must be limited to ≤ 0.5 W/kg.

For transmit RF body coils in 1.5T scanners centered outside of the area from the top of the head to L5: whole body averaged SAR must be < 2 W/kg (Normal Operating Mode).

CAUTION: *Direct exposure of the Vivistim® System to the transmit RF peripheral coil must be avoided. Scans of the body (torso) performed using a transmit RF peripheral coil are strictly prohibited.*

CAUTION: *Scans performed with the RF coil centered in the C7 – T12 area must have the whole body averaged SAR limited to ≤ 1.5 W/kg for 3T scans and ≤ 0.5 W/kg whole body averaged SAR for 1.5T scans. Scans in this area at SAR levels higher than this are strictly prohibited.*

22.10.3 Extremity Scans

MRI scans of extremities are permissible using 1.5T or 3T transmit/receive RF peripheral coils. Scan conditions specified in Table 22.2 and Table 22.3 of this manual must be met.

For transmit RF peripheral coils in 1.5T and 3T scanners: scans shall be performed in Normal Operating Mode which limits the SAR appropriately.

CAUTION: *Direct exposure of the Vivistim® System to the transmit RF peripheral coil must be avoided. Scans of extremities performed using a transmit/receive RF peripheral coil results in minimal or no exposure of the Vivistim® System to RF energy.*

CAUTION: *Certain MR system peripheral RF coils operate in receive-only mode and require the use of a transmit RF body coil. The use of a receive RF peripheral coil does not alter hazards of the transmit RF body coil.*

22.11 Consideration for a Partially Explanted Vivistim® System (Remnant Leads)

22.11.1 MRI Safety Information

Non-clinical testing has demonstrated that remnants of MicroTransponder's Model 3000 Leads less than 5cm are MR Conditional. A patient with this remnant can be safely scanned in an MR system using a transmit RF body coil and meeting the following conditions:

- Static magnetic field of 1.5 Tesla (1.5T) or 3 Tesla (3T)
- Maximum spatial static magnetic field gradient of 5,000 G/cm (50.0 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2.0 W/kg (Normal Level Operating Mode) for 1.5T and 3T scanners
- Maximum length of remnant Lead cannot exceed 5 cm. MRI should not be performed if the IPG has been removed and the remaining lead length is any length of 5cm or greater (up to and including a fully intact lead with no IPG connected).

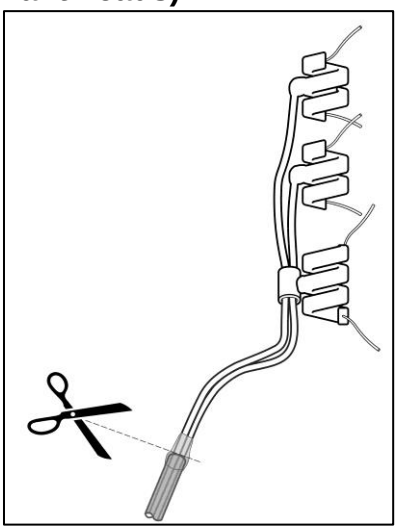


Figure 22.3: Example of a Remnant Lead

- If a remnant portion remains in a patient needing an MRI then a safe length of lead segment remaining (i.e., ≤ 5 cm) can be assessed by taking an x-ray.

Under the defined scan conditions, MicroTransponder's Model 3000 Lead remnants are expected to produce a maximum temperature rise of less than 6.0 ºC after 15 minutes of continuous scanning.

CAUTION: *The RF heating behavior does not scale with static field strength. Devices that do not exhibit detectable heating at one field strength may exhibit high values of localized heating at another field strength.*

In non-clinical testing, the image artifact caused by MicroTransponder's Model 3000 Lead remnant extends approximately 1.9 cm from the Lead when imaged with a spin-echo pulse sequence in a 3T MRI system and is less in a 1.5T MRI system.

22.12 Preparation Prior to MRI Examination

- No transmit RF head or transmit RF peripheral coil can be placed over any component of the implanted Vivistim® System. Inform the patient of all the risks associated with undergoing an MRI examination as stated in this manual.
- A trained professional with the proper knowledge of MRI equipment such as an MRI-trained radiologist must ensure the MRI examination will be conducted according to the information outlined in this manual.
- If the patient has other active medical device implants, the patient must be made aware that additional risks may occur, as potential interaction with the Vivistim® System has not been evaluated.
- Patient must see their physician prior to undergoing an MRI examination to perform the following:
  - Perform a Lead Impedance Check. Do not perform an MRI if the Lead impedance is greater than 10 kΩ.
  - Program Magnet Mode OFF
  - Document the patient's programmed parameters.
  - Program the Amplitude (mA) to 0.0 mA
- Do not conduct an MRI if the implanted Lead is not connected to the IPG (a Lead surgically cut no farther than 5 cm from the most distal tip of the electrodes may be safely MRI-scanned per the conditions of this manual).

- Do not conduct an MRI with any non-implantable component of the Vivistim® System in the MRI scan room, including the Wireless Transmitter, SAPS software, and surgical accessories. Off-the-shelf accessories such as the magnet are considered MR Unsafe and are also to be left outside of the MRI scan room. These could become dangerous flying objects if attracted by the strong magnetic field of the MRI scanner.
- If possible, do not sedate the patient so the patient can inform the MRI operator of any problems during the examination.
- Instruct the patient to immediately inform the MRI operator if any discomfort, stimulation, shocking, or heating is experienced during the subsequent scan.

22.13 Considerations During the MRI Examination

Carefully monitor the patient throughout the MRI examination both visually and audibly. Discontinue the MRI examination immediately if the patient cannot respond to questions or reports any problems.

22.14 Considerations After the MRI Examination

- Turn the device on and restore the IPG to pre-MRI settings.
- Confirm that the IPG has been restored to pre-MRI settings.
- Confirm the IPG communicates and reports a Lead impedance <10 kΩ.

23 Information and Support

MicroTransponder, Inc.
2802 Flintrock Trace, Suite 226
Austin, TX 78738
www.microtransponder.com
info@microtransponder.com

24 Glossary

AE (adverse event)—Any symptom, sign, illness, or experience that develops or worsens in severity and/or frequency during the course of the study (i.e., any changes from baseline).

BOL (beginning of life)—This the state of the battery when the first therapy session is initiated that is used to project the lifetime of the battery.

Chronic Stroke — According to agreed definitions for the timeline of stroke recovery developed by the Stroke Recovery and Rehabilitation Roundtable workforce (Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. Bernhardt J, et. al. Neurorehabil Neural Repair. 2017 Sep;31(9):793-799.) - ≥6 months post stroke is generally considered chronic.

D02 clinical study (depression study) and E01 through E05 (epilepsy studies)—Clinical trials conducted by Cyberonics. The D02 study used VNS Therapy® in patients with chronic or recurrent treatment-resistant depression. The E01 through E05 used VNS Therapy® in patients with refractory epilepsy. VNS Therapy® stimulates the vagus nerve at stimulation settings somewhat similar to Paired VNS™, except that there is no pairing with rehabilitation like is done with Paired VNS™. Also, Paired VNS™ typically only occurs for about 90 minutes in a session, while VNS Therapy® typically stimulates 24 hours a day.

Electrode—The mechanical and electrical interface of the Vivistim® System to the vagus nerve. The electrode is part of the Lead.

EMI—Electromagnetic interference

EOL (end of life)—The SAPS software displays an EOL indicator when there is less than 5% of the battery remaining. EOL indicates that the IPG will cease to function in the very near future.

ERI (Elective Replacement Indicator)—The SAPS software displays an ERI indicator when there is less than 15% of the battery remaining. This is a warning to the user that the IPG is quickly approaching EOL and may stop functioning in the near future.

High Lead Impedance—For the purposes of the Paired VNS™ IFUs, any impedance above 10,000 Ω is considered high. Resistance to the flow of output current produced by the IPG, caused by any of the following: possible fibrosis between the nerve and electrode, dry nerve (during surgery), Lead fracture, Lead disconnection from the IPG, or high battery impedance approaching end of life (EOL).

IPG (Implantable Pulse Generator) —The stimulator portion of the Vivistim® System, typically implanted in the chest below the clavicle. The IPG provides stimulation to the vagus nerve through a connected Lead and Lead electrodes.

Lead—An implantable part of the Vivistim® System; delivers electrical impulses from the IPG to the electrodes attached to the vagus nerve; contains flexible conductive wires within a bio-compatible insulating sheath.

Low Lead Impedance—Lower than expected resistance to the flow of output current produced by the IPG potentially caused by a short-circuit condition resulting from a break within the Lead body or connector boot.

MRI—Magnetic resonance imaging

MR Conditional—Item that has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use.

MR Unsafe—An item that poses hazards in all MRI environments.

Output current—Amount of electrical current delivered in a single pulse of stimulation, measured in mA.

Paired VNS™—VNS delivered by the Vivistim® System. The Vivistim® System pairs VNS with movements during standard rehabilitation therapy.

Pulse width—Duration of a single pulse within a train of stimulation, measured in µs.

Safe Mode—an IPG firmware mode initiated when the firmware determines an error that could affect proper delivery of therapy. Therapy is not possible while the IPG is in Safe Mode. A reset function must be performed to enable therapy.

SAE (serious adverse event)—Any adverse event that resulted in any of the following outcomes: death, a life threatening adverse experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or any medical intervention that prevents one of the above.

SAPS (Stroke Application & Programming Software)—Software that allows the clinician or clinic personnel to set the VNS settings and initiate stimulations paired with rehabilitation.

Signal frequency—Repetition rate of pulses in a stimulation; measured in number of pulses per second (Hz).

Signal "off" time—Interval between stimulations when there is no stimulation; measured in minutes.

Signal "on" time—Length of time the programmed output current is delivered; measured in seconds.

Train—Duration (in seconds) that the signal frequency is output from the IPG.

Vagus nerve—Either of the pair of tenth cranial nerves arising from the medulla and supplying mainly the viscera, especially with autonomic sensory and motor fibers.

Vivistim®—Trade name of the Vivistim® System for upper extremity motor deficits associated with stroke.

VNS—Vagus Nerve Stimulation

VNS Therapy®—VNS delivered by Cyberonics' VNS Therapy® System. Paired VNS™ is delivered by the MicroTransponder's Vivistim® System.

WT (Wireless Transmitter)—An RF device that connects via a USB plug to the laptop's USB port and provides communication with the IPG, used in conjunction with SAPS.