The Genio® System 2.1 (Implantable Stimulator Model #2954) – Surgeon Manual

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician

Patented and design protected technology.

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Table of Abbreviations

AC	Genio® Activation Chip
AHI	Apnea-Hypopnea Index
AIMD	Active Implantable Medical Device
App	Application
BMI	Body Mass Index
CU	Genio® Charging Unit
DP	Genio® Disposable Patch
EMC	Electromagnetic Compatibility
ENT	Ear, Nose and Throat
ES	Genio® External Stimulator
EtO	Ethylene Oxide
HGN	Hypoglossal Nerve
IS	Implantable Stimulator
MRI	Magnetic Resonance Imaging
OR	Operating Room
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PS	Power Supply
RF	Radiofrequency
RFID	Radiofrequency Identification

1 Introduction

1.1 About the Surgeon Manual

The Genio® System 2.1 is intended for use under direct supervision of a licensed healthcare practitioner or by personnel trained in its proper use. This manual contains detailed information on device function, system setup, implant, explant and revision/replacement procedures, and includes information on potential risks and follow-up care. Implant, explant and revision/replacement of the device must be performed by a qualified surgeon trained by Nyxoah-authorized personnel.

This Surgeon Manual applies to Genio® Implantable Stimulator Model #2954 (IS # Model #2954). The Implantable Stimulator Model #2954 was approved based on clinical trial data obtained using the 1st Generation model of the Implantable Stimulator, which is a similar but not identical device (see Section 3). A side by side visual representation of both models of the Implantable Stimulator can be found in Figure 1 below.

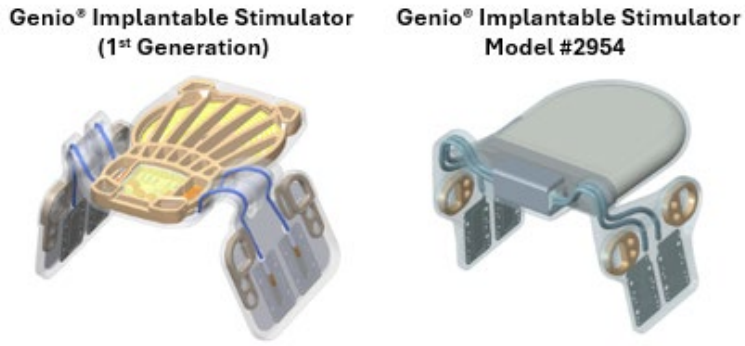


Figure 1. Side by Side Illustration of Implantable Stimulator Models

1.2 Therapy Overview

1.2.1 Genio® System 2.1 Overview

The Genio® System 2.1 (see Figure 2) comprises of a bilateral Genio® Implantable Stimulator, which is implanted via a single incision surgical procedure and positioned over the genioglossus muscle with its electrodes facing both left and right hypoglossal nerve branches. Stimulation of the hypoglossal nerve causes the tongue muscles to contract with the intention to maintain an open airway.

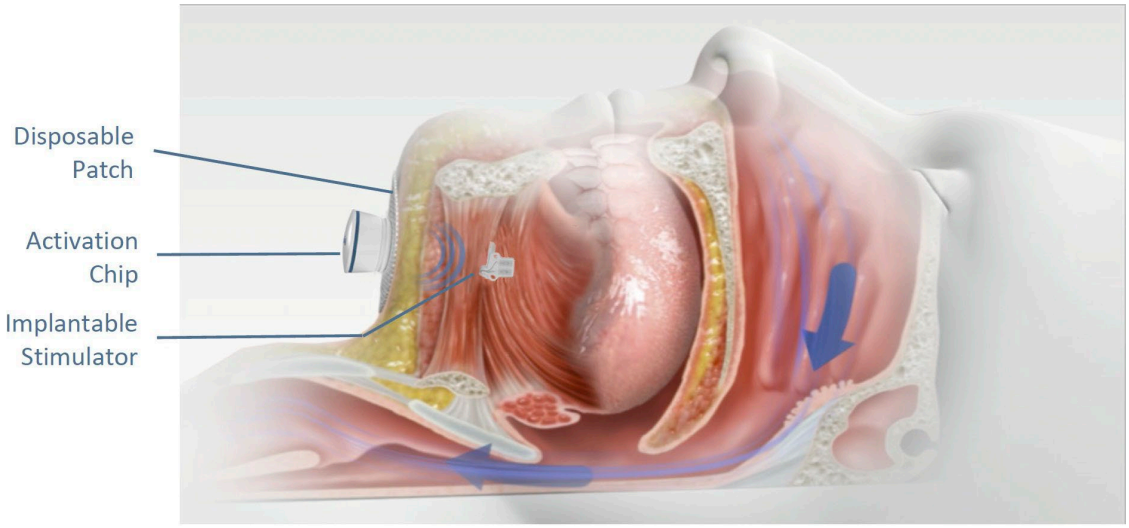


Figure 2: Genio® System 2.1 technology Overview

The Implantable Stimulator receives energy pulses transmitted by a Genio® Activation Chip which is attached to an adhesive Genio® Disposable Patch and placed on patient's skin under the chin. The Activation Chip, containing the patient's stimulation parameters and a rechargeable battery, is programmed wirelessly using a Genio® Sleep Lab Application (Sleep Lab App). To activate the therapy, the patient connects the Disposable Patch to the Activation Chip and places it under the chin every night before going to sleep. To discontinue the stimulation, the AC is removed in the morning, followed by the removal of the Disposable Patch. The battery of the Activation Chip will be recharged during the day using the Charging Unit.

During the implant procedure, surgeons use external devices (i.e., a Genio® External Stimulator and the Activation Chip/Disposable Patch combination) to activate the Implantable Stimulator verifying its functionality and optimal placement.

1.2.2 Genio® System 2.1 Stimulation Parameters

The stimulation parameters used for Genio® therapy are controlled by the Activation Chip and configured in the sleep lab using the Sleep Lab App. These parameters include pulse amplitude, frequency, duration as well as stimulation train parameters such as train length (on time) and train interval (off time). The pre-defined range for the stimulation parameters is established by Nyxoah field personnel in accordance with direction provided by the sleep physician. Using the optional Smartphone App, the user also has the ability to fine tune the amplitude, within a pre-defined limit.

Table 1 below lists the configured stimulation parameters values and limitations for the Genio® System 2.1 along with a description of which user(s) can modify each parameter and how.

Table 1. Genio® System 2.1 Activation Chip Stimulation parameter ranges, steps and default values

Treatment Parameter	Description	Available Range (step)	Default Setting	Who Can Modify the Parameter and How?
Pulse Length	Duration of one stimulation pulse	50-250 µsec (10µsec)	100 µsec	Nyxoah Field Personnel (via Sleep Lab App)
Pulse Frequency	Pulse repetition rate within stimulation train	30-50 Hz (5Hz)	30 Hz	Nyxoah Field Personnel (via Sleep Lab App)
Train Length	Duration of stimulation train	0.2-5sec (0.1sec)	1 sec	Nyxoah Field Personnel (via Sleep Lab App)
Train Interval	Duration of pause between stimulation trains	0.2-5sec (0.1sec)	4 sec	Nyxoah Field Personnel (via Sleep Lab App)
Treatment Amplitude	Stimulation amplitude	1-100 % (1%)	1%	Nyxoah Field Personnel (via Sleep Lab App) Patient (via Smartphone App, only within the boundaries set by Nyxoah Field Personnel)
Lowest Amplitude Limit	Stimulation amplitude bottom limit for Smartphone application	1-100 % (1%)	1%	Nyxoah Field Personnel (via Sleep Lab App)
Highest Amplitude Limit	Stimulation amplitude top limit for Smartphone application	1-100 % (1%)	1%	Nyxoah Field Personnel (via Sleep Lab App)
Delay time	Time between the connection of the AC-DP and the start of the stimulation therapy	5-60 min (5min)	30 min	Nyxoah Field Personnel (via Sleep Lab App)
Ramp Up duration	Time for stimulation amplitude ramp up within train (linear distribution).	0 -1000 msec (50msec)	0 - Not active	Nyxoah Field Personnel (via Sleep Lab App)
Hold Time Duration	Duration time after reaching train amplitude target prior to step-down execution	0 – 500 msec (50msec)	0 - Not active	Nyxoah Field Personnel (via Sleep Lab App)
Step down Target amplitude	Stimulation amplitude step reduction within a pulse	1 - 100% (1%)	0 - Not active	Nyxoah Field Personnel (via Sleep Lab App)
Ramp at stimulation Onset	Time for stimulation amplitude ramp up between trains (linear distribution) during the treatment initiation.	0-30 min (5min)	0 - Not active	Nyxoah Field Personnel (via Sleep Lab App)

The stimulation parameters described in Table 1 above are illustrated in Figure 3 through Figure 5 below. These figures provide a visual representation of the IS stimulation pulses delivered to the HGN when triggered by the radiofrequency (RF) energy sent from the AC. Figure 3 illustrates the train length, train interval, pulse amplitude, pulse frequency and pulse duration stimulation parameters. The amplitude ramp up within each train setting is depicted in Figure 4 while the stimulation ramp up at therapy initiation setting parameters are shown in Figure 5.

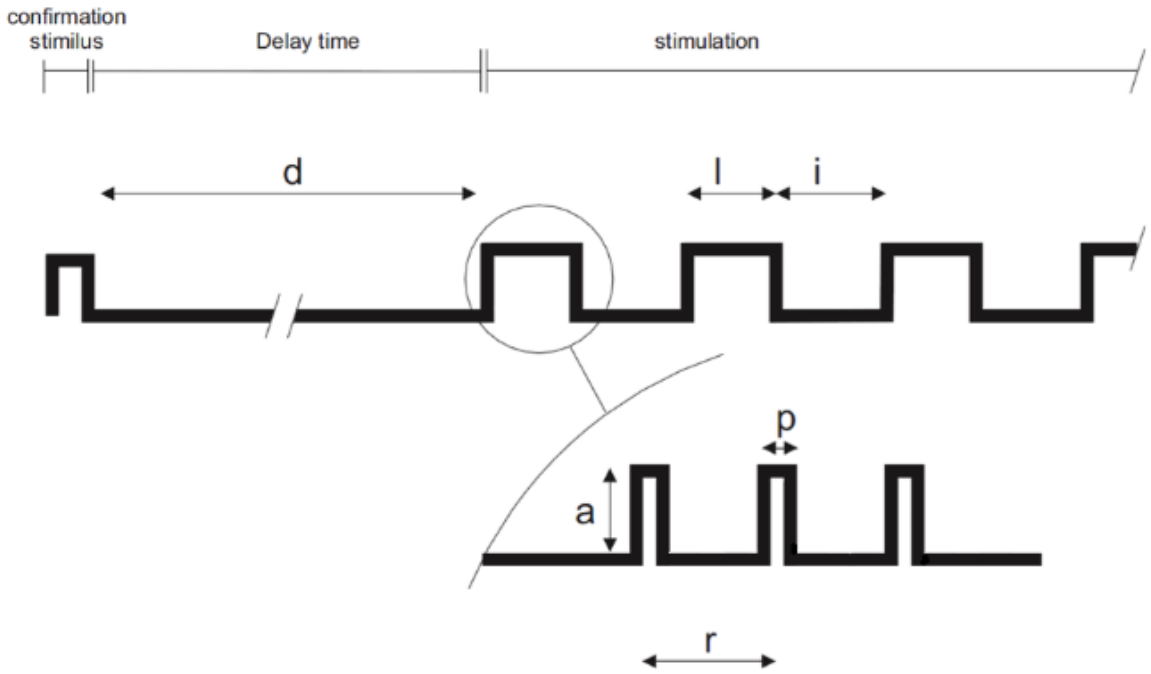


Figure 3. Illustration of Genio® System 2.1 stimulation parameters
(l = train length, i = train interval, a = treatment amplitude, r = pulse frequency, p = pulse duration, d = delay time)

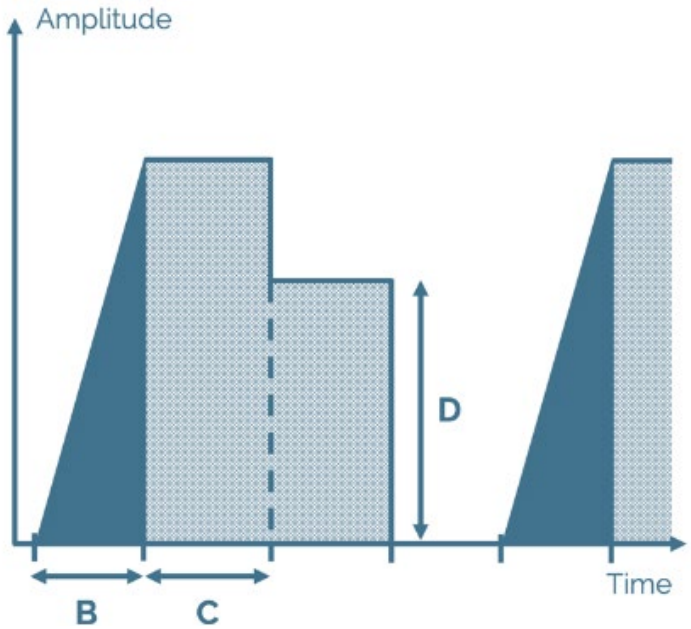


Figure 4. Amplitude ramp up within each train pulse setting parameters
(B = ramp up duration, C = hold time duration, D = step down target amplitude)

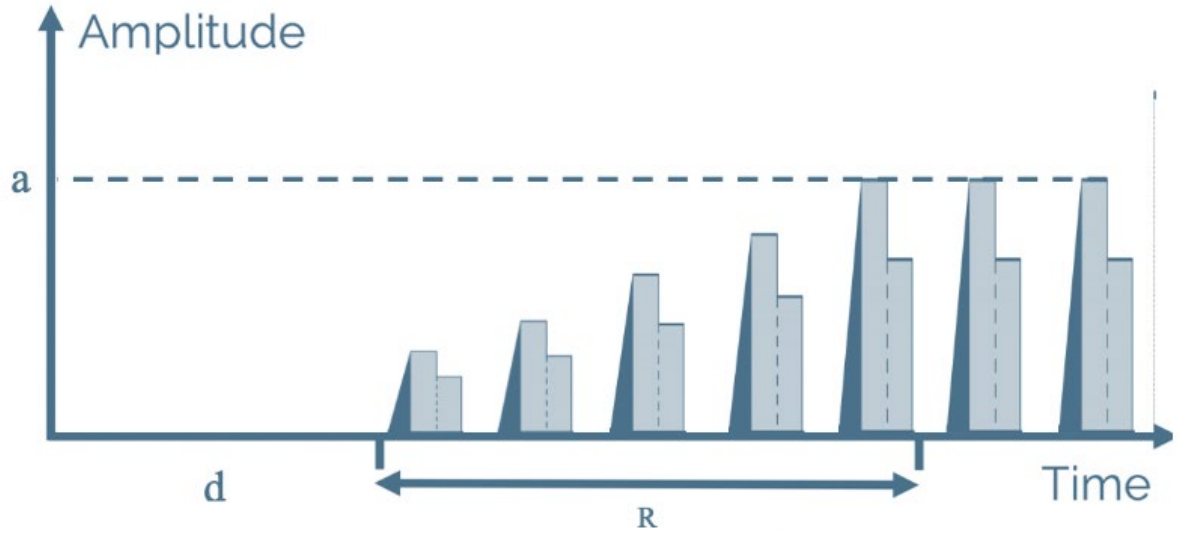


Figure 5. Stimulation ramp-up at the therapy initiation setting parameters
(a = treatment amplitude, d = delay time, R = ramp at stimulation onset)

1.2.3 Genio® Therapy Optimization

Optimization of the Genio® therapy is achieved through observation of a patient's physiological response to therapy while awake, under Drug-Induced Sleep Endoscopy (DISE), and while the patient sleeps using the therapy. The effectiveness of the Genio® System 2.1 stimulation parameters is measured by AHI indicator through the use of a Home Sleep Test (HST) and attended polysomnography (PSG) while the patient sleeps using the therapy. Nyxoah field personnel use attended PSGs to allow for real-time evaluation and titration of Genio® therapy by observing the patient's respiratory response to the therapy. The Nyxoah field personnel responsible typically have a background in field clinical engineering and always work under the guidance of a qualified healthcare professional.

Determination of the optimal therapy settings for a patient is achieved by applying Sher criteria to the PSG results. Sher criteria is defined as (at least) a 50% reduction in AHI with the residual AHI below 20 events/hr. The titration process can differ from patient to patient. Stimulation parameters can be changed multiple times until the patient acclimates to the stimulation and therapeutic efficacy is obtained. All changes made to a patient's stimulation parameters during any of the above-mentioned procedures is always done under the guidance of a healthcare provider (HCP). While changes to stimulation parameters controlled by Nyxoah field personnel cannot be done remotely, patients do have the ability to self-titrate the stimulation amplitude within a pre-defined range via the Smartphone App (see Table 1 for more details).

2 Safety Information

2.1 Indications for Use

The Genio® System 2.1 is indicated for use in the treatment of moderate to severe Obstructive Sleep Apnea (OSA) (apnea-hypopnea index [AHI] of greater than or equal to 15 and less than or equal to 65). The Genio® System 2.1 is intended for adults 22 years of age and older who have been confirmed to fail, cannot tolerate or are ineligible to be treated with current standard of care treatments including lifestyle modifications, positive airway pressure (PAP) treatments (such as continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP] machines, oral appliances (such as mandibular advancement devices), and pharmacotherapy (such as tirzepatide).

PAP failure is defined as an inability to eliminate OSA (AHI of greater than 15 despite PAP usage), and PAP intolerance is defined as:

1. Inability to use PAP (greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night), or
2. Unwillingness to use PAP (for example, a patient returns the PAP system after attempting to use it).

2.2 Patient Evaluation

In evaluating patients as candidates for Genio® therapy, in addition to conducting a general physical exam, the surgeon should perform a standard head and neck examination that includes the oral cavity as well as the neck. The surgeon should document the tonsil size and note the Mallampati score along with any findings such as neck scars that may indicate past surgery or trauma to the neck. The patient should also be evaluated for normal tongue function.

The findings from the overall patient evaluation should be used to inform the decision on whether a patient is a good candidate for Genio® therapy. In addition to consideration of the Genio® System 2.1 contraindications, warnings and precautions which apply to certain patient populations, certain functional and/or structural characteristics noted during the patient's anatomical evaluation should be factored in when assessing patient eligibility. Examples include the following:

- **Tonsil Size:** While patients with a Brodsky grade 3 or 4 tonsil size are not absolutely contraindicated for the Genio® System 2.1, consideration should be given to alternative therapies available to the patient (e.g., tonsillectomy) based on the benefit that such interventions may provide. If there are absolute contraindications to tonsillectomy, the patient refuses tonsillectomy, or the surgeon judges that the patient would benefit more from therapy with the Genio® System 2.1 than from a tonsillectomy, patients with Brodsky grade 3 or 4 tonsil size may be considered for Genio® therapy. The effectiveness of Genio® therapy in these patients has not been studied.

- **Mallampati Score:** While it has not been correlated with candidacy related to hypoglossal nerve stimulation (HNS) therapy, the Mallampati score or Friedman tongue position can be correlated with outcomes related to uvulopalatopharyngoplasty. As such, noting this score may help inform the surgeon as to whether the patient is a poor candidate for anatomy altering surgery such as uvulopalatopharyngoplasty and may be better served utilizing HNS (e.g., Genio®) therapy.
- **Surgical Scars/Masses:** Surgical scars or masses may be relative contraindications if the patient has had a past surgery or trauma in the area where the Genio® Implantable Stimulator will be implanted that could make surgical dissection more challenging.
- **Tongue Function:** If a patient has evidence of weakness of the tongue on one side or the other, it is possible that Genio® therapy would not be as effective on the side with the weakness. While pre-existent tongue weakness is not an absolute contraindication for the Genio® System 2.1, the surgeon should exercise caution and counsel the patient prior to surgery that this may result in ineffective delivery of therapy.

2.3 Contraindications

The Genio® System is contraindicated for:

- Patients with combined central and mixed apnea-hypopnea index greater than or equal to 25% of the total AHI
- Patients with any functional or structural problem, medical illness or condition that would prevent or interfere with implantation, activation or continued use of the Genio® System
- Patients with implantable device which may be susceptible to unintended interaction with the Genio® system. Consult the device manufacturer to assess the possibility of interaction.
- Women who are pregnant, planning to become pregnant or breastfeeding.
- Any condition or procedure that has compromised neurological control of the upper airway.

2.4 Warnings

2.4.1 Patient Populations

Safety and effectiveness in the following groups have not been established with the Genio® System 2.1:

- Patients younger than 22 or older than 75 years of age
- Patients with a Body Mass Index (BMI) greater than 32 kg/m2
- Patients with an Apnea Hypopnea Index (AHI) less than 15 or greater than 65 events/hr
- Patients with Complete Concentric Collapse (CCC) at the soft palate level

2.4.2 Pregnancy

If a patient becomes pregnant after being implanted with the Genio® Implantable Stimulator, it is recommended they discontinue use of the Genio® System 2.1 during their pregnancy unless otherwise instructed by the health care provider overseeing care of their sleep apnea.

2.4.3 Tonsil Size

While patients with a Brodsky grade 3 or 4 tonsil size are not absolutely contraindicated for the Genio® System 2.1, consideration should be given to alternative therapies available to the patient (e.g., tonsillectomy) based on the benefit that such interventions may provide. If there are absolute contraindications to tonsillectomy, the patient refuses tonsillectomy, or the surgeon judges that the patient would benefit more from therapy with the Genio® System 2.1 than from a tonsillectomy, patients with Brodsky grade 3 or 4 tonsil size may be considered for Genio® therapy.

2.4.4 Single-Use Devices

The Genio® Implantable and Genio® External Stimulator are single-use devices. Do not resterilize or reuse.

2.4.5 Medical Treatments

Some medical treatments may interfere with or damage the Genio® Implantable Stimulator or body tissue. For example:

- Treatment of muscle and joint conditions using heating of the tissue by high frequency electric current (diathermy)
- Radiation Therapy
- Kidney stone treatment using ultrasound (lithotripsy)
- Magnetic Stimulation, or any other form of electrical stimulation
- Therapeutic ultrasound
- Treatments that use heat to destroy cancer cells (radiofrequency or microwave ablation)
- Treatment in a hyperbaric chamber
- Any medical treatments that involve the neck (this includes any cosmetic procedures involving the neck)

A health care provider should confirm that the patient's Implantable Stimulator is working as Intended after undergoing these or similar medical treatments.

2.4.6 Dental and Surgical Procedures

Patients with the Genio® Implantable Stimulator should avoid dental and surgical procedures that involve the floor of the mouth or lower jaw as this could damage or displace the implant, including:

- injections to the floor of the mouth, and
- use of retractors or other instruments that might put pressure on or lacerate the floor of the mouth mucosa

For routine surgical or dental procedures involving a patient implanted with the Genio® Implantable Stimulator, a perioperative dose of antibiotics should be administered. If during any such procedure, infection is noted, a longer course of antibiotics should be prescribed.

2.5 Magnetic Resonance (MR) Scan Safety 

The Genio® Implantable Stimulator Model #2954 is a Magnetic Resonance (MR) Conditional device which means that the implant is safe in the MR environment within certain conditions.

This section contains important information regarding the Implantable Stimulator Model #2954 and the conditions in which a patient implanted with the Implantable Stimulator Model #2954 can safely undergo an MR scan. MR scans must be performed only as described in this section.

2.5.1 MRI Technician Warnings and Precautions

- The MR scan should be conducted at least eight (8) weeks after patient implantation or revision surgery.
- Genio® System external devices (such as the Disposable Patch or Activation Chip) shall not be brought by the patient to the MR scan room and used during the MR scan. The use of the Disposable Patch and Activation Chip during an MR scan is prohibited.
- Do not scan the patient if any conditions exist which could make the MRI scan unsafe such as presence of a fever and presence of other implanted devices that prohibit safe scanning.
- During the MR scan, continuously monitor the patient for any signs of anxiety and/or discomfort. If you notice an increase in these signs, discontinue the MR scan.
- In some instances, stimulation of the tongue muscles can occur leading to uncomfortable sensation. Additionally, the patient may feel discomfort during part or all of the MR scan. If the patient feels uncomfortable pain or heating during the MR scan which is intolerable, the scan should be terminated.
- The MR scan may cause the implant to move which could lead to discomfort and/or pain for the patient.

2.5.2 Potential risks associated with MR scans

The Implantable Stimulator device has been designed to minimize the potential adverse events that could result in patient harm.

The potential MR scan-related adverse events are listed below:

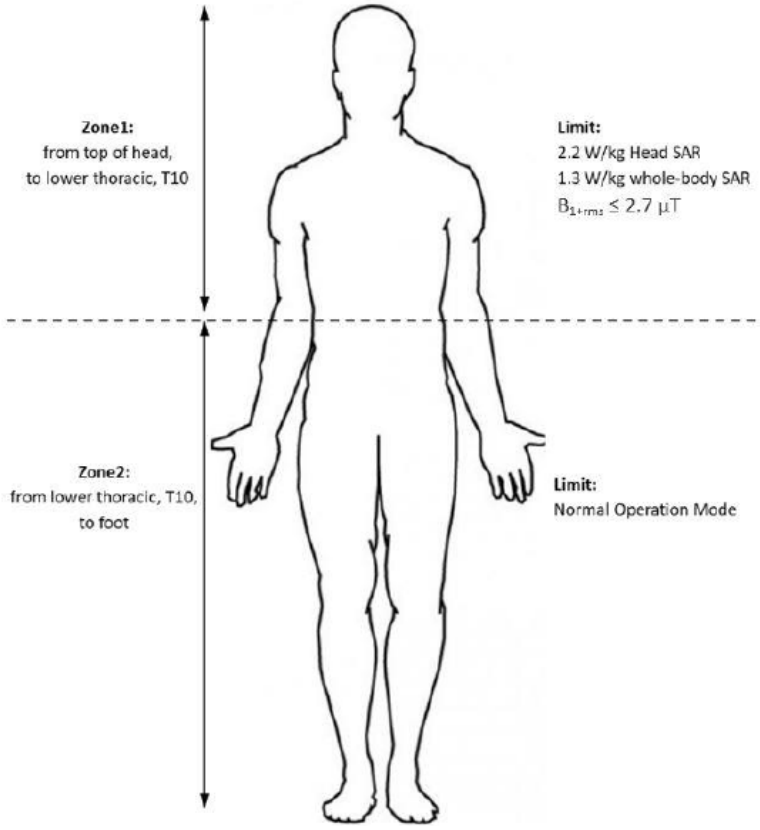
- Implant heating causing damage to tissue in contact with the implant.
- Implant migration causing damage to tissue in contact with the implant.
- Implant migration causing the implant to be surgically removed (and replaced).
- Unintended over stimulation causing damage to tissue in contact with the implant.
- Unintended stimulation causing discomfort due to electrical stimulation.
- Device malfunction causing the implant to be surgically removed (and replaced).
- Diagnostic problems due to artifacts - shadowing on the MR image in the vicinity of the implant causing loss or disturbance of diagnostic information.

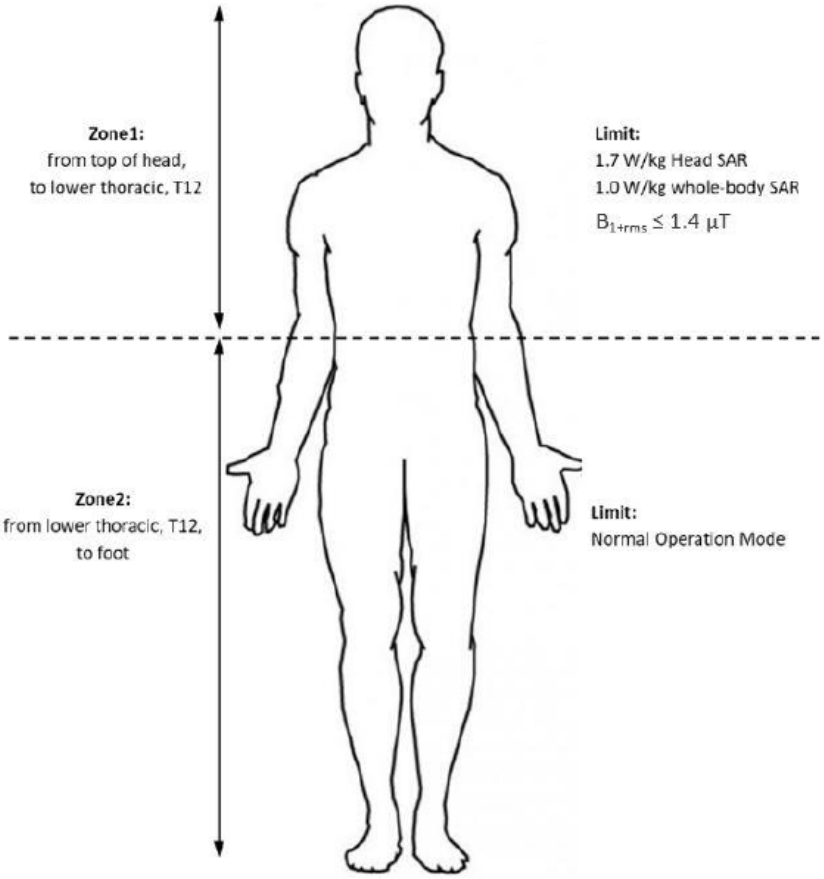
2.5.3 MR Scan Conditions

Non-clinical testing has demonstrated the Implantable Stimulator Model #2954 is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions (see Table 2):

Table 2. Genio® IS Model #2954 MR Scan Conditions

Parameter	Conditions of Use/Information
Static Magnetic Field Strength (B_0)	1.5 Tesla and 3 Tesla
Type of Nuclei	Hydrogen
Static Magnetic Field (B_0) Orientation	Horizontal, Cylindrical Bore
Maximum Spatial Field Gradient (SFG)	129 T/m (12,900 gauss/cm)
Maximum switched gradient slew rate per axis	200 mT/m/ms
Maximum switched gradient amplitude per axis	45 mT/m
RF Polarization	Circular Polarization (CP)
RF Transmit Coil Type	Integrated Whole Body Transmit RF Coil
RF Receive Coil	Any receive-only RF coil may be used
MR System (RF) Operating Modes or Constraints	Normal Operating Mode
$B_1{}^+_{RMS}$ (1.5 Tesla)	1.5 Tesla From the top of head to the lower thoracic T10 (Zone 1)**: ≤ 2.7µT** From the lower thoracic T10 to the foot (Zone 2): **limited by Normal Operating Mode**

Parameter	Conditions of Use/Information
	 Note: $B_1^+{}_{RMS}$ shall be used on all MR systems with this limitation parameters. Use SAR only on MR systems not providing $B_1^+{}_{RMS}$ limitation. Both $B_1^+{}_{RMS}$ and SAR limits must be observed.
$B_1^+{}_{RMS}$ (3 Tesla)	3 Tesla From the top of head to the lower thoracic T10 (Zone 1)**: ≤ 1.4µT** From the lower thoracic T10 to the foot (Zone 2): **limited by Normal Operating Mode**

Parameter	Conditions of Use/Information
	 Note: $B_1^+{}_{RMS}$ shall be used on all MR systems with this limitation parameters. Use SAR only on MR systems not providing $B_1^+{}_{RMS}$ limitation. Both $B_1^+{}_{RMS}$ and SAR limits must be observed.
Whole Body Averaged SAR	<u>1.5 Tesla</u> From the top of head to the lower thoracic T10 (Zone 1): **< 1.3 W/kg** From the lower thoracic T10 to the foot (Zone 2): **<2.0 W/kg** <u>3 Tesla</u> From the top of head to the lower thoracic T10 (Zone 1): **< 1.0 W/kg** From the lower thoracic T10 to the foot (Zone 2): **<2.0 W/kg**
Scan Duration and Wait Time	Scan for 60 minutes with one or more MR pulse sequences (scans or series) followed by a wait time of 15 minutes before resuming scanning.
MR Image Artifact	The presence of this implant may produce an image artifact of 19.2mm.

2.6 Precautions

2.6.1 Components

Do not use any components other than those supplied by Nyxoah for the Genio® System 2.1.

2.6.2 Defibrillation/Cardioversion

The possible interaction between the Genio® System 2.1 and cardiac devices (implantable defibrillators) has not been investigated. After defibrillation or cardioversion, a health care provider should confirm that the patient's Implantable Stimulator is working as intended.

2.7 Risks

2.7.1 Risks Associated with the Implantation Procedure

Implantation of the Genio® System is performed in an operating room and requires general anesthesia. As with any surgical procedure, there are risks associated with both surgery and anesthesia which are independent of the risks associated with the Genio® System itself. Prior to implanting, you should discuss the risks and benefits of the Genio® System – including procedure and anesthesia risks – with the patient. The patient should also be informed of alternative therapy options to ensure they have been appropriately counselled and that any questions that they may have are addressed. The implantation surgery may involve the following risks:

Very common risks (which may affect more than 1 in 10 patients):

- Post-surgical mild to moderate pain, discomfort, stiffness or tenderness at the implant site
- Post-surgical mild to moderate swelling or bruising around the implant site
- Post-surgical numbness, tingling or other sensory changes related to the skin incision

Common risks (which may affect between 1 in 10 and 1 in 100 patients):

- Post-surgical discomfort
- Impaired or painful swallowing
- Impaired or painful speaking due to the procedure
- Paresthesia (sensation of ticking or itching)
- Bleeding
- Hematoma
- Pain or irritation in the throat or nasal passage from intubation
- Dry mouth
- Post-surgical hoarse voice
- Damage or trauma to nerves, blood vessels or muscles
- Local skin irritation
- Infection
- Worsening of OSA symptoms (e.g., fatigue or sleep disturbances)

Uncommon risks (which may affect less than 1 in 100 patients):

- Post-surgical headache
- (Transient) tongue weakness or soreness
- Tongue fasciculations (twitching of tongue) or spasm
- Muscle or skin tightness
- Post-surgical pain/complication due to the position on the table during the procedure (head extension, body position)

- Temporary lip weakness
- Post-surgical fever
- Superficial skin infection
- Impaired sense of taste
- Increase or decrease in size of the tongue muscle and/or fat
- Persistent pain at the implant site
- Abnormal scarring or healing problems

2.7.2 Risks Associated with the Devices and the Use of the Devices

The potential device-related adverse events are listed below:

Very common risks (which may affect more than 1 in 10 patients):

- Temporary local skin irritation
- Impaired or painful swallowing due to the device
- Discomfort or pain due to electrical stimulation
- Mouth blisters (due to tongue rubbing against teeth during stimulation)
- Mild to moderate pain, swelling, stiffness or tenderness at the implant site or with the use of the device

Common risks (which may affect between 1 in 10 and 1 in 100 patients):

- Mild tongue abrasion
- Abnormal scarring
- Tongue fasciculations (twitching of tongue)
- Dry mouth
- Temporary tongue muscle weakness or soreness
- Temporary usability or functionality issues with an external device leading to temporary delay of treatment
- Permanent usability or functionality issues with an external device leading to no therapy
- Usability or functionality issues with the implanted device
- Increased or continued snoring
- Headache or dizziness
- Fatigue or sleep disturbances, while acclimating to stimulation
- Change in salivary flow
- Clinically significant implant migration (device moving from implanted location and potential partial or complete expulsion of the device from its intended place)
- Presence of fibrosis making the removal of the Genio® Implantable Stimulator Model #2954 difficult without damaging the surrounding structures

Uncommon risks (which may affect less than 1 in 100 patients):

- Impaired sense of taste or metallic taste
- Increased acid reflux
- Increased upper airway secretions
- Paresthesia (sensation of tickling or itching)

- Pain or irritation in the throat or nasal passage
- Allergic and/or rejection response to the implanted device
- Damage to tissue (nerves, blood vessels or muscles) in contact with the implant or in the vicinity of the implant
- Damage to tissue in contact with external devices
- Persistent pain at the implant site
- Impaired or painful speaking due to the device
- Risks related to additional surgery and any unstudied potential effect
- Cellulitis at surgical site

2.7.3 Risks Associated with Revision (Repositioning or Replacement) and Explant Procedures

If an additional surgery is performed in order to have the implant removed, repositioned, or replaced, the risks detailed above, along with some new risks, would apply to the surgery. The risks of a revision surgery are higher because scar tissue builds up around the implanted device, and there is a higher risk of infection from the surgery. Additional injury to the nearby nerves, blood vessels or tissues could occur.

2.7.4 Risks Associated with Pregnancy and Breastfeeding

The effects of the Genio® System 2.1 on the unborn child and on the new-born are not known. Because of this, a patient cannot be implanted if pregnant or trying to become pregnant, or breastfeeding.

If a patient becomes pregnant after being implanted, it is recommended the patient does not use their Genio® System during pregnancy unless otherwise instructed by their health care provider overseeing care of the patient's sleep apnea.

2.7.5 Risks Associated with Device Service Life

The patient can expect the Genio® Implantable Stimulator Model #2954 to continue working for least 12 years. Nyxoah will provide support for the device as long as the Implantable Stimulator remains in place.

The risks of using the implant beyond the timeframe mentioned above include the potential for the Genio® therapy to become less effective or stop working altogether, possibly requiring supplemental therapy solutions to treat the patient's OSA symptoms. You could also experience an allergic reaction to the materials of the device, however this risk is low. The patient should inform their health care provider if they experience any perceived changes to their Genio® therapy.

2.8 Storage and Handling

Nyxoah sterilizes the Implantable Stimulator and External Stimulator with ethylene oxide (EtO) prior to shipment. Both devices are sterile only if you received the packages intact. If the packaging is wet, punctured, opened, suspected to be contaminated or otherwise damaged, return the device to Nyxoah. Do not implant in case the packaging is damaged. Only use sterile-gloved hands to handling the External Stimulator and Implantable Stimulator. Do not use/implant an External Stimulator or Implantable Stimulator that was dropped.

WARNING: The Implantable Stimulator and the External Stimulator are single-use devices. Do not re-sterilize or reuse.

2.8.1 Storage Conditions

Keep system components stored in a clean area with room temperature of approximately +15 °C to +27 °C / +59 °F to +81 °F.

CAUTION: If any of the system components were stored at conditions outside the parameters listed above, they cannot be used and should be returned to Nyxoah for inspection.

2.8.2 Operating Temperature

The External Stimulator and Activation Chip contain an internal battery. To prevent the potential for battery overheating, the External Stimulator should only be operated at temperatures lower than 38.5°C/101.3°F and the Activation Chip should only be operated at temperatures lower than 39°C/102.2°F.

CAUTION: Do NOT operate the External Stimulator at temperatures higher than 38.5°C/101.3°F as this could cause the battery to overheat.

CAUTION: Do NOT operate the Activation Chip at temperatures higher than 39°C/102.2°F as this could cause the battery to overheat.

2.8.3 Expiration Date

Do not use the Implantable Stimulator and External Stimulator after the expiration date printed on the package label. The expiration date shows the valid shelf life of the device. The warranty is void after this date and sterility might be compromised.

2.8.4 Handling

The Implantable Stimulator should be carefully handled to avoid damage. Do not put sharp instruments in contact with the implant. Do not apply excessive force, bend or twist the implant.

2.9 Alternative Therapies

There are several other alternatives for the treatment of individuals with obstructive sleep apnea (OSA), from lifestyle changes (e.g., weight loss and positional therapy) to PAP (positive airway pressure), oral appliances, anatomical surgery and hypoglossal nerve stimulation (HGNS).

Individuals with mild to moderate OSA often use lifestyle changes alone, PAP, mandibular advancement devices (oral appliance therapy), or anatomical surgery.

The treatment alternatives for individuals with moderate to severe OSA include: PAP, mandibular advancement devices (oral appliance therapy), use of Tirzepatide (in patients with comorbid obesity contributing to pathophysiology of their OSA), anatomical surgical treatments or HGNS treatments to enlarge the airway.

Each alternative has its own advantages and disadvantages. A patient should thoroughly discuss the risks and benefits of treatment alternatives with his/her healthcare provider to select the treatment method that best meets their needs.

3 DREAM Study Results

Nyxoah performed a clinical study (“DREAM”) to evaluate the safety and effectiveness of the Genio® System to treat adult subjects with moderate to severe Obstructive Sleep Apnea (OSA) in the US, Belgium, Germany and Australia. The results of the DREAM (Dual sided hypoglossal neRvE stimulAtion for the treatMent of obstructive sleep apnea) are summarized in the sections below.

3.1 Device Under Test

The study was conducted using the 1st Generation model of the IS ("original IS"). Although the original IS and IS Model #2954 differ in certain characteristics, the two versions of the Genio® System 2.1 implant were considered functionally equivalent in key areas such as: electronic circuitry, stimulation parameters used, active stimulation area of the electrodes, mode of communication with the AC Model #2364, and use of external components. Based on all the non-clinical and pre-clinical testing conducted for IS Model #2954, it was concluded that the changes made for the IS Model #2954 did not impact the performance or functionality of the implant when compared to the original IS. Considering both the similarities between the original IS and the IS Model #2954 as well as the assessment of the design changes, the clinical data obtained with the original IS during the DREAM IDE study was considered leverageable for the IS Model #2954. An assessment of the impact any differences between the two implant models may have on the applicability of the data gathered during the DREAM clinical study has been provided in Table 3.

Table 3. Comparison of the Genio® System 2.1 Implant Used in the DREAM Clinical Study ("Original IS") and the IS Model #2954

Characteristic	Differences Between the Version of the Implant Used for the Clinical Study (Original Implantable Stimulator) and the Implantable Stimulator Model #2954	Impact of Implantable Stimulator Model #2954 Differences on Clinical Data Collected Using the Original Implantable Stimulator
Materials of construction	While there are minor differences in the materials of construction used for both versions of the implant (e.g., ceramic main body in the Implantable Stimulator Model #2954 versus Parylene coated PEEK frame in the original Implantable Stimulator), the materials with direct patient contact are the same (silicone and platinum electrodes)	No impact – the differences in the non-patient contacting materials of the original Implantable Stimulator and the Implantable Stimulator Model #2954 do not introduce were found to not pose any biological safety risks to the patient or user Results from the biocompatibility testing showed that the Implantable Stimulator Model #2954 is biologically safe to use as intended.
Thickness of main body	The main body of the Implantable Stimulator Model #2954 is slightly thicker (~1.0mm) than the original IS due to the introduction of the ceramic pouch	No impact – as the adjacent muscles (Geniohyoid and Genioglossus) are flexible, they would not be impacted by any additional thickness of the implant's main body. Results of the chronic animal study served to confirm the increase in thickness did not impact the position of the implant over time.
Average total mass	The mass increased from 3.0g to 6.15g in the Implantable Stimulator Model #2954	No impact – the paddles of the Implantable Stimulator Model #2954 are sutured into place like they are for the original Implantable Stimulator while fibrosis occurs which will further help to maintain positional stability of the implant. The positional stability of the main body of the Implantable Stimulator Model #2954 prior to fibrotic tissue formation was verified as part of chronic animal study. Results of the study showed that there was no impact to the position of the implant over time due to the increase in mass. Additionally, the Implantable Stimulator Model #2954 has increased flexibility of the connecting shoulders which reduces the exertion forces on the paddle sutures, the interface of the electrode with the HGN would not be expected to change over time due to the increase in implant mass. The reduction of forces exerted on the suturing anchors due to increase of shoulder flexibility was confirmed through a dedicated Finite Element Analysis (FEA) comparison and associated bench testing. The FEA assessed the susceptibility of paddle migration under extreme physiological loading modes both with and without fibrotic tissue. Suturing scenarios (including simulated suture rupture) were verified by supportive bench testing. Stresses and forces were evaluated for both the original Implantable Stimulator and Implantable Stimulator Model #2954. Results of the FEA and bench testing showed that due to the design changes made for the Implantable Stimulator Model #2954, the forces exerted on the suturing anchors due to implant body movement were equal to or lower than the original Implantable Stimulator across all displacement ranges, even with one suturing anchor unsecured. These tests serve to support that despite an increase in mass, there is no increase in the potential risk of migration of the Implantable Stimulator Model #2954 when compared to the original Implantable Stimulator.

Characteristic	Differences Between the Version of the Implant Used for the Clinical Study (Original Implantable Stimulator) and the Implantable Stimulator Model #2954	Impact of Implantable Stimulator Model #2954 Differences on Clinical Data Collected Using the Original Implantable Stimulator
Number of shoulders	The number of shoulders was reduced for the Implantable Stimulator Model #2954 from a double-shoulder to a single-shoulder design	No impact – the reduction of the number of shoulders (two to one) for Implantable Stimulator Model #2954 has led to an increase in the flexibility of the paddles' connective shoulders. As the electrode positioning and suturing of the paddles remains the same, the increased flexibility of the decouples the forces generated from main body movement and the forces pulling the paddles sutures, thus there would be no impact on the mechanical interface of the paddle with the nerve (i.e., no change to the clinical effects). Changes to a single shoulder design allows for easier handling and positioning of the paddles over the HGN during the implantation procedure. Results from the HF validation study done for the Implantable Stimulator Model #2954 showed that there was no impact to the ability to correctly perform the implantation procedure or properly position the implant due to the reduction of shoulders.
Width/thickness of paddle shoulders from top view at maximal height	The width/thickness of the Implantable Stimulator Model #2954 paddle shoulders (~3.15mm one shoulder width/thickness) is slightly greater than the original Implantable Stimulator (~2.48mm/2.60mm for one shoulder or ~4.96mm/5.2mm for both shoulders)	No impact – while the width/thickness of the paddle shoulders of the Implantable Stimulator Model #2954 is slightly larger for one shoulder versus the two for the original Implantable Stimulator, the difference is considered negligible relative to the change from a two-shoulder design in the original Implantable Stimulator versus a single shoulder design in the Implantable Stimulator Model #2954 (as described above).
Expected service life	The expected service life of the Implantable Stimulator Model #2954 increased to 12 years from three (3) years in the original Implantable Stimulator due to the introduction of the hermetic ceramic enclosure used for the main body	No impact – the increase in device lifetime means the Implantable Stimulator Model #2954 will need to be replaced less often. This difference does not impact the results of the clinical study.

While the clinical data obtained with the original Implantable Stimulator during the DREAM study is considered leverageable for the Implantable Stimulator Model #2954, there are two key limitations to using data from the original Implantable Stimulator to support the newer Implantable Stimulator Model #2954:

1) The method relies on empirical observations to infer the performance of an untested device in human subjects, and
2) The introduction of new design variables, although potentially enhancing performance, does not allow for a direct comparison of the two designs.

Therefore, the Implantable Stimulator Model #2954 will be further evaluated as part of the Genio® System 2.1 post-approval study.

3.2 Patients Studied

Between October 14, 2020 and March 3, 2023, the study enrolled 687 participants. These participants were evaluated against predefined patient selection criteria, which included adults with moderate to severe OSA that had failed or not tolerated Positive Airways Pressure (PAP) treatments, having a BMI less than or equal to 32, without complete concentric collapse (CCC) at the soft palate level (evaluated by performing a Drug Induced Sleep Endoscopy [DISE]). A total of 568 subjects did not meet these criteria; 2 patients were not implanted due to study enrollment closing, and 2 other patients were not implanted due to lack of site staff resources. Implant was attempted in a total of 115 subjects with 113 of them being successfully implanted with the Genio® system. The results were analyzed in all 115 patients (Intent-To-Treat, ITT population) and in 110 patients (modified Intent-To-Treat, mITT population) that successfully completed the implant procedure. An additional 3 patients were also not included because their data was unmonitored. A total of 88 patients completed the 12 months without major (critical) deviations (Per-Protocol population). All patients that did not have results at 12 months were treated as non-responders.

Table 4 summarizes the patient demographics for the study.

Table 4. Patient Demographics

Demographic / Participant Characteristics	Mean ± SD (N = 115)	Median (Min; Max)
Age, year	56.8 ± 7.3	57 (36;71)
Male, gender	70.4% (81/115)	
Body Mass Index, kg/m^2	28.50 ± 2.63	28.7 (21.7; 32.0)
BP Systolic, mmHg	132.6 ± 16.5	131
BP Diastolic, mmHg	79.9 ± 10.0	80
Neck Circumference, cm	40.55 ± 5.73	40.6 (30.5; 86.4)
Race: Caucasian	93.9% (108/115)	NA
Race: Asian	0.9% (1/115)	NA
Race: Black or African American	3.5% (4/115)	NA
Race: Other	1.7% (2/115)	NA
OSA Characteristics	**Mean ± SD (N = 110)**	
AHI events/h	28.00 ± 11.47	
ODI events/h	26.95 ± 13.78	
Medical History	**n (%)**	
Hypertension	47 (40.9%)	
Gastroesophageal reflux disease (GERD)	34 (29.6%)	
Depression	28 (24.3%)	
Hypercholesterolemia	25 (21.7%)	
Hyperlipidemia	21 (18.3%)	
Anxiety	21 (18.3%)	

3.3 Study Objectives and Methods

The DREAM study was a multicenter, prospective, single-arm study. Patients were scheduled for screening and baseline evaluations before implant and follow-up post-surgery at 2, 3, 4, 5, 6, 8 and 10 months or 9 months, and a final follow-up at 12 months.

Effectiveness was evaluated by two co-primary endpoints:

- percentage of responders at 12 months based on AHI4, a responder being defined as a participant who satisfies the following criteria: at least a 50% reduction from the average AHI4 of screening and baseline to 12 months post-surgery and a remaining AHI4 less than 20 at the 12-month visit (aka “Sher Criteria”).
- percentage of responders at 12 months based on ODI4, a responder being defined as a participant who satisfies the following criterion: at least a 25% reduction from the average ODI4 of screening and baseline to 12 months post-surgery.

There were six secondary effectiveness endpoints, focusing on: OSA-specific quality of life measured by the SNORE-25 instrument; hypoxemic burden measured by the percentage of sleep time with oxyhemoglobin saturation< 90%; intermittent hypoxia measured by the ODI4; the sleep-specific function measured by the Functional Outcomes of Sleep Questionnaire (FOSQ-10); the sleep propensity measured by the Epworth Sleepiness Scale (ESS) and change in OSA severity.
Safety was evaluated by the incidence of device-related serious events (SAEs) recorded during the study for a period of 12 months post-surgery. Adverse events (AEs) were adjudicated by an independent Clinical Events Committee (CEC). An independent Data & Safety Monitoring Board (DSMB) reviewed the accumulated safety data and the validity and integrity of the data from the clinical study.

3.4 Safety results

Out of the 115 patients in whom implant was attempted, 85 (73.9%) experienced a total of 252 non-serious device and/or implant procedure-related AEs (see Table 5 through Table 7). The non-serious procedure-related AEs observed were anticipated with this type of surgery including difficulty swallowing/dysphagia (11.7% of patients) and swelling at the incision site (12.2% of patients). Among the device-related non-serious events, 24.3% of patients experienced local skin irritation due to the Disposable Patch (DP), 14.8% of patients reported discomfort with the stimulation, and 12.2% experienced tongue discomfort. The same patient can experience various effects.

Table 5. Implant Related Adverse Events

	Number of subjects	Percentage of subjects
Incision site swelling	14	12.2%
Incision-related (hypoesthesia, hematoma, ingrown hair, paraesthesia, foreign body, pain, irritation, reaction, dermatitis, application site infection)	13	11.7%
Dysphagia	12	10.4%
Temporary tongue weakness (speech disorder, dysarthria, tongue movement disturbance)	10	9.0%
Post procedural pain (oropharyngeal pain, odynophagia, ear discomfort, glossodynia)	10	9.0%

	Number of subjects	Percentage of subjects
Post surgical effects (fever, headache, anxiety, fatigue, discomfort, diarrhea, nausea)	9	8.1%
Anesthesia related (phlebitis, presyncope, dysphonia, cough, glossitis)	8	7.2%
Implant site hypoesthesia	7	6.1%
Procedural pain	7	6.1%
Post procedural contusion	6	5.2%
Miscellaneous (epistaxis, ageusia, jaw clicking, tinnitus)	5	4.5%
Post procedural swelling	3	2.6%
Implant site infection	1	0.9%
Tongue spasm	1	0.9%

Table 6. Device Related Adverse Events

	Number of subjects	Percentage of subjects
Application site irritation	28	24.3%
Stimulation discomfort	17	14.8%
Glossodynia	14	12.2%
Tongue complications (discomfort, spasm, swollen, involuntary contractions, tongue abrasions, plicated tongue)	9	7.8%
Incision site-related (swelling, hemorrhage, site reaction)	8	7.0%
Other symptoms (dizziness, dyspepsia, gastroesophageal reflux, panic attack, tinnitus)	8	7.0%
Dysphagia	7	6.1%
Pain (jaw, ear, oropharyngeal, neck)	6	5.2%
Application site reaction (rash)	5	4.3%
Medical device pain	4	3.5%
Glossitis	3	2.6%
Dysphonia	2	1.7%
Headache	2	1.7%
Somnolence, Sleep disorder	2	1.7%
Cough	1	0.9%

	Number of subjects	Percentage of subjects
Hypoesthesia oral	1	0.9%
Jaw disorder	1	0.9%
Application site ulcer	1	0.9%
Tooth disorder	1	0.9%
Sensation of foreign body	1	0.9%

Table 7. Device and Implant - Related Adverse Events

	Number of subjects	Percentage of subjects
Dysphagia	2	1.7%
Back pain	1	0.9%
Cough	1	0.9%
Medical device pain	1	0.9%
Musculoskeletal discomfort	1	0.9%
Neck pain	1	0.9%
Oropharyngeal pain	1	0.9%
Pain in jaw	1	0.9%
Sleep disorder	1	0.9%
Somnolence	1	0.9%

Serious Adverse Events

Table 8 provides the summary of all SAEs through 12 months post-implantation.

Table 8: SAE Summary through 12 Months Post Implant – SAF Set (N=115)

Serious Events	m (n,%)
Unrelated to Genio® Device and Unrelated to Implant Procedure – Serious Adverse Events (SAE)	3 (2, 1.7%)
Genio® Device-Related and/or Implant Procedure-Related – Serious Adverse Events (SAE)	13 (13, 11.3%)*
• Genio® Device-Related	6 (6, 5.2%)*

Serious Events	m (n,%)
• Genio® Implant Procedure-Related	6 (6, 5.2%)*
• Genio® Device and Implant Procedure-Related	1 (1, 0.9%)*

n: number of subjects with at least one event
% = (n row / N column x 100)
m: number of events
Note: A same subject can have more than one event
* The 13 serious adverse events include 1 case of repositioning surgery (procedure related) and 4 cases of replacement surgery (device-related) that were neither classified by the Study Investigators nor by the Clinical Events Committee (CEC) as serious adverse events. If these events are excluded from the list of SAEs, the overall incidence of device- and/or procedure-related SAEs up 12-months would be 7% (device-related: 1.7%, device- and procedure-related: 0.9%, procedure-related: 4.3%).

Table 9 provides the description of device and/or procedure related SAEs through 12 months post-implant to date.

Table 9. Serious Adverse Events 12 Months Post Implant – Safety Set (N=115)

Description of SAE	Detailed Event Description
Incision Site Hematoma	Two days post-implant surgery, patient had developed hematoma at the surgical incision site with increased neck swelling and worsening bruising of the neck requiring surgical evacuation of the hematoma. The event was resolved without sequelae 4 days later. Patient continued in the study through the 18-month visit.
Dysphagia	Patient reported inability to swallow while in the recovery room post-implant and was discharged 11 days later in stable condition. The patient exited the study 10 days after discharge with the event ongoing and opted to keep the device implanted.
Dysphagia	Patient experienced impaired swallowing on the day of implant surgery. Hospital stay was extended due to trouble related to speech and swallowing from poor tongue motion. Edema was noted at the floor of the mouth edema. The event was fully resolved without sequelae a month later and assessed. Patient remains active in the study through the M36 visit.
Epistaxis	Patient experienced epistaxis on the right side 5 days post-implant surgery and was admitted to the emergency room with intermittent nasal bleeding from abrasions secondary to attempted nasal intubation during the implant surgery. The patient was discharged 2 days later; however, intermittent nasal bleeding persisted for approximately 50 days after discharge. Event was fully resolved without sequelae. The patient remained in the study until the M24 visit and was exited 4 months after with the device kept implanted.

Description of SAE	Detailed Event Description
Bundle Branch Block Left	Patient developed ventricular ectopy and new left bundle branch block at the end of the implant surgery procedure. The patient was admitted for cardiac monitoring and discharged the next day with the event fully resolved without sequalae. Patient remained active in the study through the M18 visit and was exited from the study 2 months later due to lost to follow-up with the device kept implanted.
Device Dislocation (Explant Surgery at 8 months)	Patient experienced a lack of stimulation approximately 253 days post implant surgery. A revision surgery was performed and the Implantable Stimulator (IS) was found to have migrated to one side. Due to the tight space between the hyoid bone and mandible, replacement or revision was not possible and the device was explanted without further complications. Patient exited the study a few months later.
Device Extrusion (Explant Surgery at 10 months)	Patient reported the Implantable Stimulator (IS) was protruding through the back of the gum approximately 310 days post implant surgery. Two months prior to this event, patient underwent a planned dental implant procedure to the floor of the mouth which was followed by a significant change in the stimulation amplitude. The IS was surgically removed about 2 weeks later without complications. Patient exited the study 3 weeks post explant surgery.
Device Dislocation (Explant Surgery at 2 months)	Patient reported increased swelling under the chin without pain, approximately 2 months post-implant surgery and reported no sensation or physical response to stimulation. X-ray showed disoriented and migrated device. Patient underwent explant surgery a month later without complications. Patient exited the study 2 weeks post-surgery.
Replacement Surgery at 6 Months *	Patient experienced inconsistent stimulation with suspected retrusor branch of the HGN included during implant as the Investigator did not observe straight tongue protrusion. During surgical intervention no migration was identified but excessive scarring was noted, preventing replacement. Device was explanted without complications.
Replacement Surgery at 6 Months *	Patient reported stimulation discomfort and intermittent stimulation. External component troubleshooting revealed atypical device activity. During surgical intervention it was confirmed the device had not migrated. The device was successfully replaced without complication with consistent stimulation observed from new device during intra-operative testing. Patient continued in the study.
Replacement Surgery at 11 Months *	Patient experienced inconsistent stimulation that could not be resolved with external component troubleshooting. During surgical intervention the device was tested with no response. Device was successfully removed and replaced with consistent stimulation observed from new device during intra-operative testing. Patient continued in the study.
Replacement Surgery at 12 Months *	Patient experienced loss of stimulation that could not be resolved with external component troubleshooting. Migration noted in X-ray with migration of right paddle confirmed during intervention. Excessive scarring prevented replacement and device was explanted without complications.

Description of SAE	Detailed Event Description
Repositioning Surgery at 9 Months *	Patient had mixed hypoglossal nerve activation on the left noted when the device was activated. The Investigator repositioned the device to exclude retrusor branches from receiving stimulation.

* The 1 case of repositioning surgery and 4 cases of replacement surgery were neither classified by the Study Investigators nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events.

Post-Month 12 Safety Data

A subset of active study subjects have completed 24-month and 36-month timepoints as shown in Table 10 below.

Table 10. Summary of Study Subjects with Post M12 Study Timepoints

Months	Subjects
24-Month	74
36-Month	30
48-Month	0

A summary of safety events post-Month 12 has been provided in the Table 11 below.

Table 11. Adverse Event Summary Post-Month 12 up to April 30, 2025

Adverse events	Non-device-related Non-procedure-related m (n, %)	Device or Procedure-related m (n, %)
Non-serious	97 (46, 40.0%) (AE)	29 (22, 19.1%) (AE)
Serious	11 (5, 4.3%) (SAE)	5 (5, 4.3%) (SAE)

n: number of subjects with at least one event

% = (n row / N column x 100)

m: number of events

Note: A same subject can have more than one event

* The 5 serious adverse events include 2 cases of replacement surgery and 3 cases of explant surgery that were neither classified by Study Investigators nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events.

Table 12 below presents a summary of all serious adverse events related to surgical interventions experienced by subjects in the DREAM study presented by month of intervention (up to April 30, 2025).

Table 12. Serious Adverse Events Related to Surgical Interventions Post-Month 12 *

Post-Surgical Intervention	Reason for Surgical Intervention	Surgical Intervention / Complications	Surgical Outcome	Subject Disposition
Explant Surgery at 17 Months	Device Deficiency: Subject feeling inconsistent stimulation. Unable to resolve with external component troubleshooting. Investigator and patient decided to explant device.	During the intervention, it was confirmed that the device had not migrated. Device tested and no stimulation observed. Device explanted without complication.	The device was successfully explanted.	No adverse events observed or reported post-operatively.
Explant Surgery at 22 Months	Device Deficiency: No stimulation felt. Unable to be resolved through external component troubleshooting. Decision was made to explant.	The device was explanted without complication.	The device was successfully explanted.	No adverse events observed or reported post-operatively.
Explant Surgery at 28 Months	Device Deficiency: Inconsistent connectivity of device. External component troubleshooting did not resolve the issue which led to deeming it to be IS related. The subject elected to have the device explanted.	During the intervention, calcification was noted on the body of the device. The device was removed without complication.	The device was successfully explanted.	No adverse events observed or reported post-operatively.
Replacement Surgery at 16 Months	Device Deficiency: Potential migration of the device after MVA. Following the incident, subject experienced inconsistent stimulation. Unable to resolve with external component troubleshooting.	Migration confirmed during intervention. Scaring and encapsulation were present, device replaced successfully with no complications.	Consistent stimulation observed from new device during intra operative testing.	Subject continued in the study. No adverse events observed or reported post-operatively.
Replacement Surgery at 21 Months	Device Deficiency: Subject feeling inconsistent stimulation.	The device was successfully replaced without complications.	Consistent stimulation observed from new device	No adverse events observed or reported post-operatively.

	Unable to resolve with external component troubleshooting.		during intra – operative testing.	

* The 5 serious adverse events include 2 cases of replacement surgery and 3 cases of explant surgery that were neither classified by the Study Investigators nor adjudicated by the Clinical Events Committee (CEC) as serious adverse events.

3.5 Efficacy Results

The efficacy of OSA symptom reduction was evaluated through two main parameters: the apnea hypopnea index (AHI) and the oxygen desaturation index (ODI). All the sleep studies were scored by an independent core laboratory, and the patient was required to sleep a minimum of 4h, with at least 1h being in the supine position.

At the 12-month post-implant PSG, the AHI responder rate was 63.5% (73/115), and the ODI responder rate was 71.3% (82/115) with a median reduction of 70.8% in AHI and 72.1% in ODI (Table 13). The improvement occurred in all sleeping positions, which reflected in the non-supine and supine AHI of 12.7±12.8 events/hr and 48.9±19.6 events/hr, respectively (n=110) being reduced to 5.2±8.2 events/hr and 22.7±19.9 events/hr (n=89, p<0.001). In summary, overall median AHI reduction (70.8%), median reduction in supine (66.6%) and median AHI reduction in non-supine (71.0%) sleep positions were comparable.

Table 13. Effectiveness Results

Primary Endpoint	Responder Rate	*p* value
AHI Response Rate M12	63.5% (73/115)	0.002
ODI Response Rate M12	71.3% (82/115)	< 0.001

Additionally, OSA symptoms and quality of life were assessed with questionnaires: 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10) and the Epworth Sleepiness Scale (ESS) questionnaire. The average scores at 12 months showed clinically relevant improvement in both symptoms and quality of life (Table 14).

Table 14. Secondary Effectiveness Endpoints

	Baseline (N=110) Mean ± standard deviation	Month 12 (N=89) Mean ± standard deviation
SNORE-25 total score	1.61 ± 0.88	0.59 ± 0.62
Total sleep time SaO2 < 90% (min)	45.18 ± 45.83	18.02 ± 30.34
Oxygen Desaturation Index (ODI) (events/hour)	26.95 ± 13.78	9.15 ± 9.60
FOSQ-10 total score	15.92 ± 2.94	18.19 ± 1.94
ESS total score	9.64 ± 5.56	6.22 ± 4.12
Apnea-Hypopnea Index (AHI) (events/hour)	28.00 ± 11.47	9.52 ± 9.43

Subgroup analyses for gender, age, race, and BMI segmented by OSA severity were performed and can be found in Table 15. In all subgroup analyses, except for the one based on race, there was a significant overlap in the confidence intervals of the various groups. This overlap confirms that there are no significant differences in treatment responses among the different subgroups.

Table **15**. Percentage of AHI and ODI at Month 12 for the various subgroups

Subgroups		**Percentage of Responders at Month 12 – Full Analysis Set (N=110) Worst Case Imputation**			
		n	n (%) of imputed missing values	Rate (n /N) of participants with 50% Reduction in AHI from baseline and AHI < 20 [95% CI]	Rate (n /N) of participants with 25% Reduction in ODI from baseline [95% CI]
Gender	**Male (N=78)**	78	16 (20.5%)	62.8% (49/78) [51.1% ; 73.5%]	71.8% (56/78) [60.5% ; 81.4%]
	Female (N=32)	32	5 (15.6%)	75.0% (24/32) [56.6% ; 88.5%]	81.3% (26/32) [63.6% ; 92.8%]
Age	**Age<52 (N=26)**	26	8 (30.8%)	53.8% (14/26) [33.4% ; 73.4%]	65.4% (17/26) [44.3% ; 82.8%]
	52≤Age≤62 (N=58)	58	10 (17.2%)	72.4% (42/58) [59.1% ; 83.3%]	79.3% (46/58) [66.6% ; 88.8%]
Race	**White (N=104)**	104	21 (20.2%)	64.4% (67/104) [54.4% ; 73.6%]	73.1% (76/104) [63.5% ; 81.3%]
	Black or African American (N=4)	4	0 (0.0%)	100.0% (4/4) [39.8% ; 100.0%]	100.0% (4/4) [39.8% ; 100.0%]
	Other (N=2)	2	0 (0.0%)	100.0% (2/2) [15.8% ; 100.0%]	100.0% (2/2) [15.8% ; 100.0%]
BMI	**BMI≤25 (N=15)**	15	4 (26.7%)	66.7% (10/15) [38.4% ; 88.2%]	66.7% (10/15) [38.4% ; 88.2%]
	25<BMI≤28 (N=34)	34	5 (14.7%)	73.5% (25/34) [55.6% ; 87.1%]	85.3% (29/34) [68.9% ; 95.0%]
	28<BMI≤30 (N=27)	27	5 (18.5%)	59.3% (16/27) [38.8% ; 77.6%]	70.4% (19/27) [49.8% ; 86.2%]
	30<BMI≤32 (N=30)	30	7 (23.3%)	63.3% (19/30) [43.9% ; 80.1%]	70.0% (21/30) [50.6% ; 85.3%]
	BMI>32 (N=4)	4	0 (0.0%)	75.0% (3/4) [19.4% ; 99.4%]	75.0% (3/4) [19.4% ; 99.4%]

3.6 Conclusion

The DREAM study results supported FDA approval of the Genio® device for the treatment of adults with moderate to severe OSA, in both supine and non-supine sleep positions, who have not tolerated, failed or refused PAP therapy.

3.7 Safety and Effectiveness Data from OUS Post-market Clinical Follow-up Study (EliSA)

Upon CE Mark approval of the Genio® System, Nyxoah initiated the EliSA trial, a post market

clinical follow up (PMCF) study. The purpose of this study is to assess the long-term safety and performance of the Genio® System and to identify any potential new risks not previously encountered during the pivotal study. Data was collected under normal conditions of use.

The EliSA study includes collection of performance related data (e.g., change of AHI, change of ODI, etc.) as well as safety data (collection of adverse events and device deficiencies). The primary and secondary outcomes for the EliSA study differ from those used for the DREAM study (i.e., change in AHI vs. responder rates). Additionally, the inclusion and exclusion criteria in EliSA allows for the enrollment of patients more severe OSA symptoms (higher mean AHI with fewer restrictions on co-morbidities or exclusionary medications) and those with a higher BMI level than what was allowed in the DREAM study.

The EliSA study aims to include 110 implanted patients with a 5-year follow-up period. As of December 12th 2024, 101 patients have been implanted in Germany, the Netherlands, Belgium and Switzerland. The enrollment is still ongoing, and currently, only 57.3% (n=63) of the subjects have completed the month 12 follow-up. A total of six (6) SADEs and 184 ADEs (183 confirmed by the CEC) have been reported[1].

The preliminary results from the EliSA study are provided in Table 16 below. The responder rate based on Sher criteria (Table 17) and the line plot showing baseline and final AHI (Figure 6) are also provided.

Table 16. EliSA preliminary AHI and ODI results for subjects completing month 12 follow-up

EliSA preliminary results	Screening (Mean±SD)	M12 (Mean±SD)	Mean change (Mean±SD)	% change (Mean±SD)
AHI (N=63)	36.1±14.2	24.7±17.1	-11.4±15.8	-30.5±40.1
ODI (N=62)	31.8±15.2	25.5±17.1	-6.3±15.9	-16.0±50.5

Table 17. EliSA preliminary responder rates for subjects completing month 12 follow-up

Responder Rates	
AHI Responder	41.3%
AHI Sher Responder	38.1%
ODI Responder	51.6%
AHI responder = 50% improvement from screening AHI Sher responder = 50% improvement + residual AHI < 20 ODI responder = 25% improvement from screening	

[1] Note that the CEC adjudication is ongoing and hence the AE classification is subject to modification

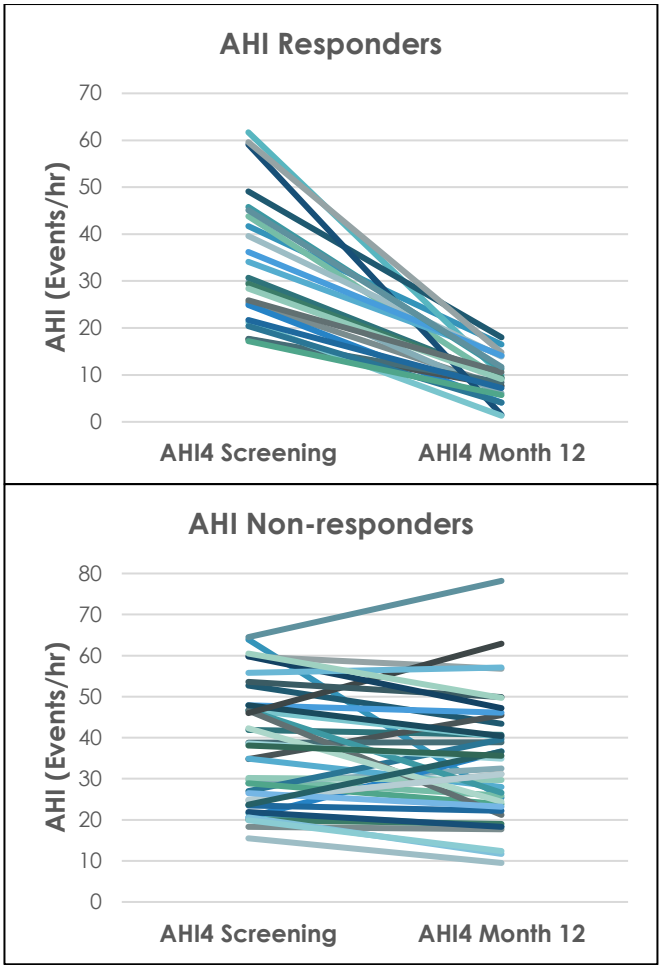


Figure 6. Line plot showing preliminary data for baseline and final AHI for EliSA study subjects (responders and non-responders) completing month 12 follow-up

As described previously, the data presented for the EliSA study is preliminary as there was no planned interim analysis defined apriori in the study protocol. The study was conducted in a real-world setup where patients were afforded fewer (just one mandatory PSG) opportunities to be titrated to optimal therapy response through a full night PSG prior to their 12-month visit. Moreover, the titration algorithm of Genio® therapy has been refined since these patients were implanted as witnessed by the improvement in responder rate in the DREAM study.

4 Surgical Components of the Genio® System 2.1

The surgical components of the Genio® System 2.1 are the Implantable Stimulator Model #2954, Surgical Template and External Stimulator. Additionally, the Implantable Stimulator will be activated with the Activation Chip/Disposable Patch (hereafter 'AC/DP') combination to verify optimal implant placement.

4.1 The Genio® Implantable Stimulator Model #2954

The Implantable Stimulator Model #2954 (see Figure 7) is a single-use, sterile, small implant that delivers stimulation to both branches of the hypoglossal nerve (i.e. left and right). The body of the Implantable Stimulator consists of an energy receiving antenna and an electrical circuit, both encapsulated in a ceramic housing, and two lateral paddles, each composed of a pair of electrodes. The Implantable Stimulator is implanted under the chin through a single incision surgical procedure. The Implantable Stimulator is designed to sit like a "saddle on a horse" over the genioglossus muscle with its paddle electrodes facing both left and right hypoglossal nerve branches. Following a simple surgical approach, the device is fixed and remains in place over time using 4 surgical ties. The Implantable Stimulator is the only implantable component of the Genio® System 2.1.

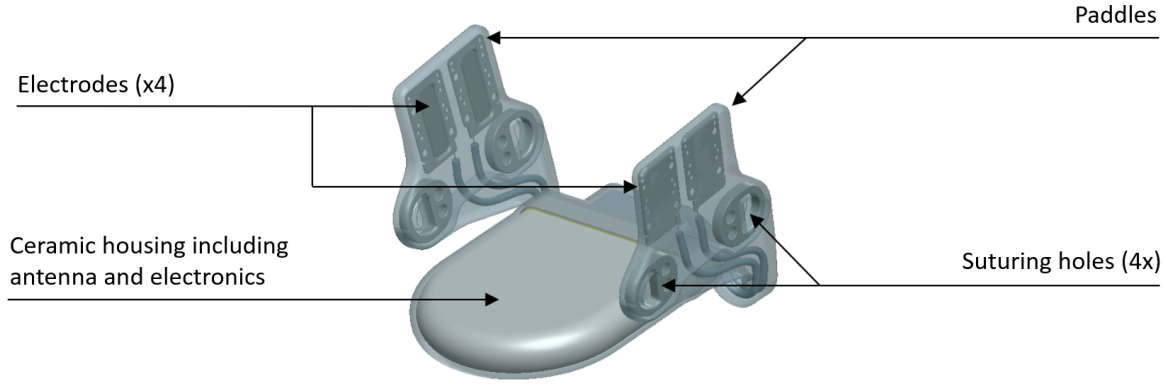


Figure 7: Genio® Implantable Stimulator

4.2 Surgical Template

The Surgical Template (see Figure 8) is a single use sterile implantation accessory made **only** of clinical grade silicone. The Surgical Template is an exact silicone replica of the Implantable Stimulator used for several purposes listed below:

- It serves as a template for sizing of the dissected areas that will accommodate the Implantable Stimulator paddles, minimizing manipulation of the implant.

- Its electrodes' windows (see Figure 8, left) mimic the areas where the paddle electrodes are positioned and can be used to verify proper hypoglossal nerve branches selection using the intraoperative neuromonitoring system.

- The clear silicone (see Figure 8, right) allows for visibility of the terminal fibers of the hypoglossal nerve affirming proper device placement.

The surgical template is not permanently implanted and is disposed of after being replaced by the Implantable Stimulator.

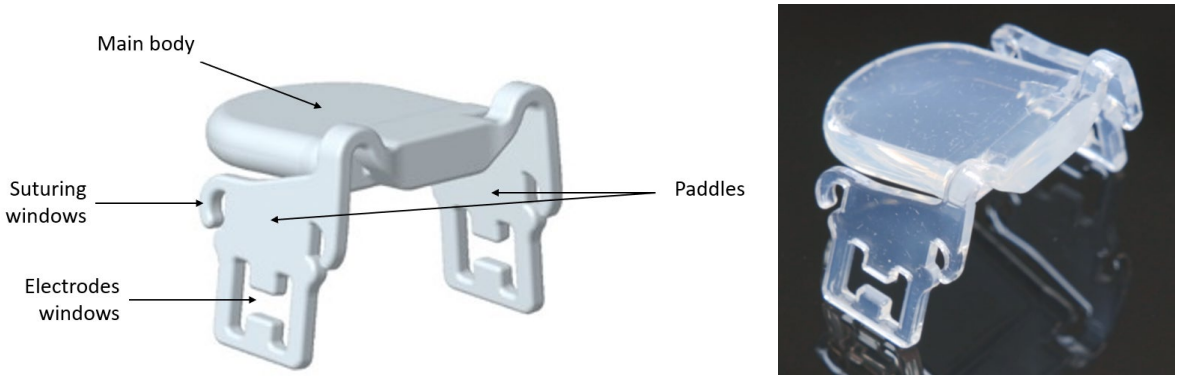


Figure 8: Surgical Template[2]

4.3 The Genio® External Stimulator

The External Stimulator (see Figure 9) is a single-use, sterile accessory. The External Stimulator allows the surgeon to activate the Implantable Stimulator during surgery to verify the implant's functionality and its optimal placement. Implantable Stimulator placement adjustments are made until proper stimulation response is reached. The External Stimulator contains a power button with LED indicator, a pre-charged battery and a retractable scaling mechanism to modify the stimulation intensity to the implant. Battery operation time is at least 60 minutes.

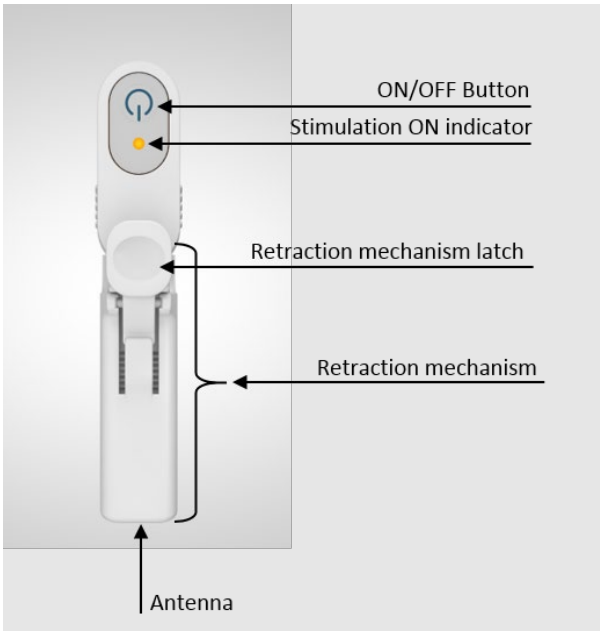


Figure 9: Genio® External Stimulator

[2] The left picture is a drawing of the Surgical Template, for reference only. The right picture shows the actual template.

The External Stimulator RF output is pre-defined and consists of the following parameters (Table 18):

Table 18. Genio® System 2.1 External Stimulator RF output parameters

Parameter	Description	Value
Pulse Duration	Duration of one stimulation pulse	200 [µsec]
Pulse Frequency	Number of pulses per second	50[Hz]
Train Length	Duration of stimulation	1[sec]
Train Interval	Duration of pause between stimulation	1[sec]
Pulse Amplitude	Stimulation amplitude	100%

Figure 10 and Figure 11 provide an overview of the stimulation output delivered by the Implantable Stimulator when activated by the External Stimulator at a minimal distance from the Implantable Stimulator:

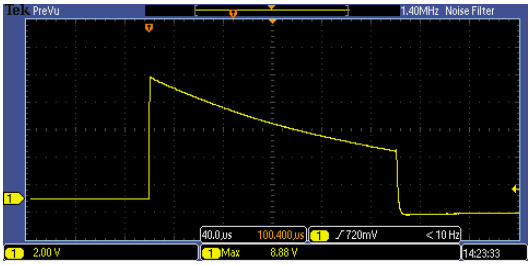


Figure 10: Single Stimulation Pulse generated by the External Stimulator

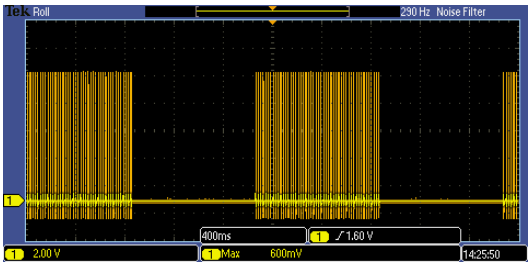


Figure 11: Stimulation Train generated by the External Stimulator

4.4 The Genio® Activation Chip and Disposable Patch

The Activation Chip is a microprocessor that contains a rechargeable Li-Ion battery, electronics for Bluetooth communication and electromagnetic power transmission and memory for storage of stimulation parameters.

The Disposable Patch is a single-use biocompatible adhesive patch. It is comprised of a flexible Printed Circuit Board (PCB) (the antenna) and an adhesive patch made of porous, highly breathable, elastic multilayered polyurethane/synthetic nonwoven material laminated with a hypoallergenic, pressure sensitive adhesive.

The Activation Chip fits onto the Disposable Patch (see Figure 12) and allows the activation of the Implantable Stimulator by transferring energy wirelessly.

Additional testing for verification of positive anatomical response and optimal Implantable Stimulator placement is completed by using the Activation Chip connected to a Disposable Patch. This AC/DP combination is placed into a sterile sleeve or sterile camera bag and used to verify the Implantable Stimulator placement. The AC/DP combination allows for specific programmed parameter settings to be tested.

NOTE: An appropriate stimulation response is symmetric protrusion of the tongue at least past the lower incisors with no obvious retraction or twisting of the tongue.

Figure 12: Activation Chip and Disposable Patch

5 Implantable Stimulator Implantation Procedure

5.1 Overview of the Procedure

Before beginning the implantation procedure, become familiar with all the equipment and instruments involved in this surgical procedure. Only certified surgeons who Nyxoah implant training can implant the Implantable Stimulator.

5.2 Surgical Materials

This procedure requires standard ENT surgical equipment used during neck surgeries. The following is a list of additional materials that shall be brought to the Operating Room (OR) for an implantation procedure (the list includes back-up devices):

- Two Genio® Implantable Stimulator Model #2954 kits (each kit includes one IS and one surgical template)
- Two Genio ® External Stimulators
- One fully charged Genio® Activation Chip
- One Genio® Charging Unit, including power adapter
- Genio® Disposable Patches
- One Genio® Sleep Lab Kit
- Braided non-absorbable sutures 2-0

WARNING: Do not use bioabsorbable sutures for the suturing of the IS. Use of bioabsorbable sutures will result in the IS becoming loose over time and could lead to implant migration and loss of device functionality.

- Atraumatic forceps and/or clamps
- A neuro monitoring system
- A sterile sleeve or sterile camera cover

5.3 Preparation and Positioning

- Patient should be in a supine position. While the patient is under general anesthesia, expose the submental region by placing the patient's head in hyperextension.
- Ensure the tongue is visible to observe response to the intraoperative stimulation tests.
- A neuro monitoring system is installed (mandatory) to locate and differentiate the medial (inclusionary) and lateral (exclusionary) branches of the hypoglossal nerve:
    - Place neuromonitoring electrodes into the left and right genioglossus muscles: into the floor of the mouth, just lateral to the midline with the electrodes pair perpendicular to the anterior mandible (see blue electrode on Figure 13). Stimulation of the medial branch of the hypoglossal nerve will be monitored based on genioglossus muscle activity.
    - Place neuromonitoring electrodes bilaterally in the styloglossus muscles: along the lateral aspect of the tongue, in the mucosa at a shallow angle, ~3-5 cm away from the tip of the tongue (see red electrode on Figure 13). Stimulation of the lateral branch of the hypoglossal nerve will be monitored based on styloglossus and hyoglossus muscles activity.
    - Suture all 4 neuromonitoring electrodes in place to ensure secure placement and stability throughout the implant procedure.
- Nyxoah field staff will set up the Genio® Sleep Lab Application and verify the Activation Chip is sufficiently charged.

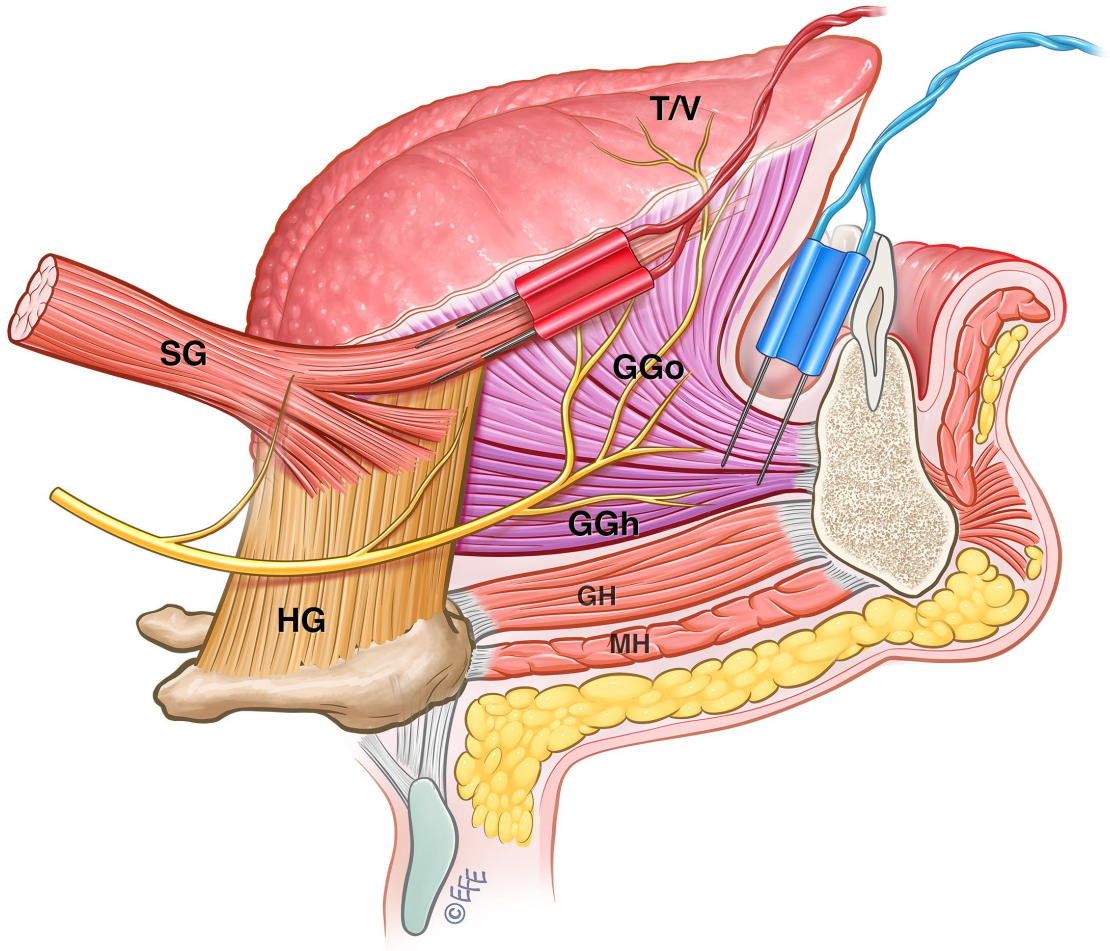


Figure 13: Intraoperative neuromonitoring system electrodes placement into genioglossus (blue electrode) and styloglossus (red electrode) muscles.

5.4 Implantable Stimulator Implantation

WARNING: Use of electrocautery should be avoided, but in case required the following guideline should be followed: Electrocautery should be used in bipolar mode. Specific attention should be paid not to put the tip in direct contact with the implant. Following the use of electrocautery in the chin/neck area once the implant is placed, a device check is recommended.

Use standard infection prophylaxis techniques to lower the risk of infection. These techniques may include but are not limited to the use of sterile prep/drape, pre-operative antibiotics, etc.

NOTE: Infections related to system implantation might require the device to be explanted.

5.4.1 Skin Incision

- Identify the hyoid bone, the mandible and the midline from mentum to hyoid bone.
- Make a 6 cm incision approximately 1 cm above the estimated location of the hyoid bone 3cm to the right and left of the midline (see Figure 14).
  NOTE: It is recommended to draw landmarks in order to define the correct position of the incision and for keeping the midline.

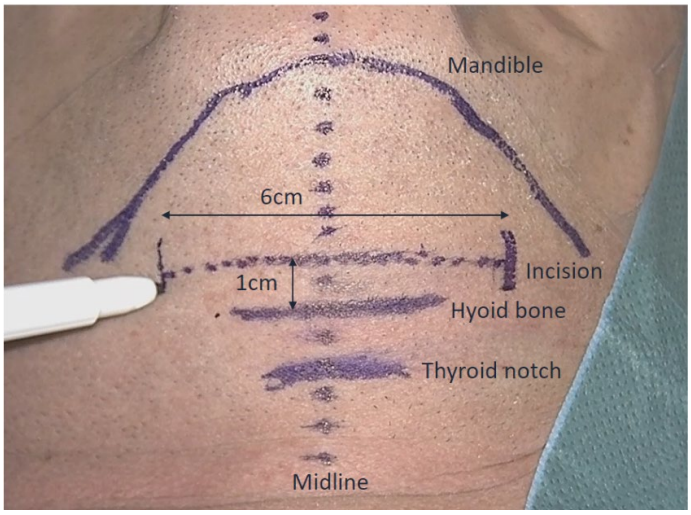


Figure 14: Landmarks

5.4.2 Reaching the Genioglossus Muscle

- Dissect through the platysma and develop the superior and inferior sub-platysma flaps.
- If visible, retract the digastric muscles.
- Identify the mylohyoid muscle. While keeping the midline, dissect through the mylohyoid muscle and expose the geniohyoid muscle (see Figure 15).

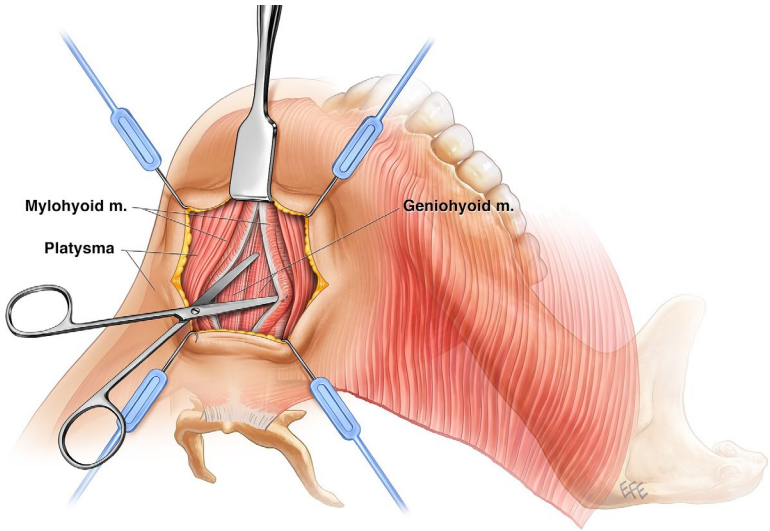


Figure 15: Dissection of the Mylohyoid to the Geniohyoid muscle

- Dissect through the geniohyoid muscle along the midline and retract laterally to expose the fatty raphe of the genioglossus muscle (see Figure 16).

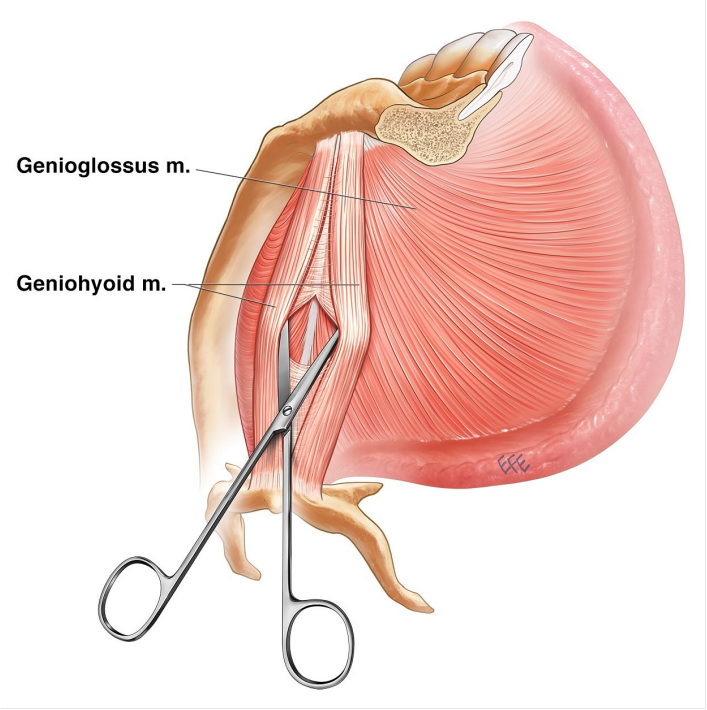


Figure 16: Dissection of the Geniohyoid to the Genioglossus muscle

5.4.3 Exposure and Identification of Hypoglossal Nerve Branches

- Dissect both lateral borders of the genioglossus muscle to reveal the branches of the hypoglossal nerve.
- Use the intraoperative neuromonitoring system signals and resulting in-situ muscle contraction to locate the main trunk of the hypoglossal nerve.
- Once identified, follow the hypoglossal nerve distally and visually track the medial branch as it enters into the genioglossus muscle (see Figure 17, “m-HGN”).
- Use the intraoperative neuromonitoring system signals and resulting in-situ genioglossus and hyoglossus muscle contractions to differentiate the medial (inclusionary) and lateral (exclusionary) branches of the hypoglossal nerve (see Figure 18).

NOTE: Stimulation of the medial branch (see Figure 17, “m-HGN”) results in genioglossus in-situ contraction and neuromonitoring activity.

NOTE: Stimulation of the lateral branch (see Figure 17, “l-HGN”) results in hyoglossus in-situ muscle contraction and hyoglossus/styloglossus neuromonitoring activity.

- Create a dissection area along the right and left lateral borders of the genioglossus muscle between the most distal lateral branch and the medial branches of the hypoglossal nerve (see Figure 18). These dissection areas will accommodate the Implantable Stimulator paddles, with its electrodes facing the inclusionary fibers.

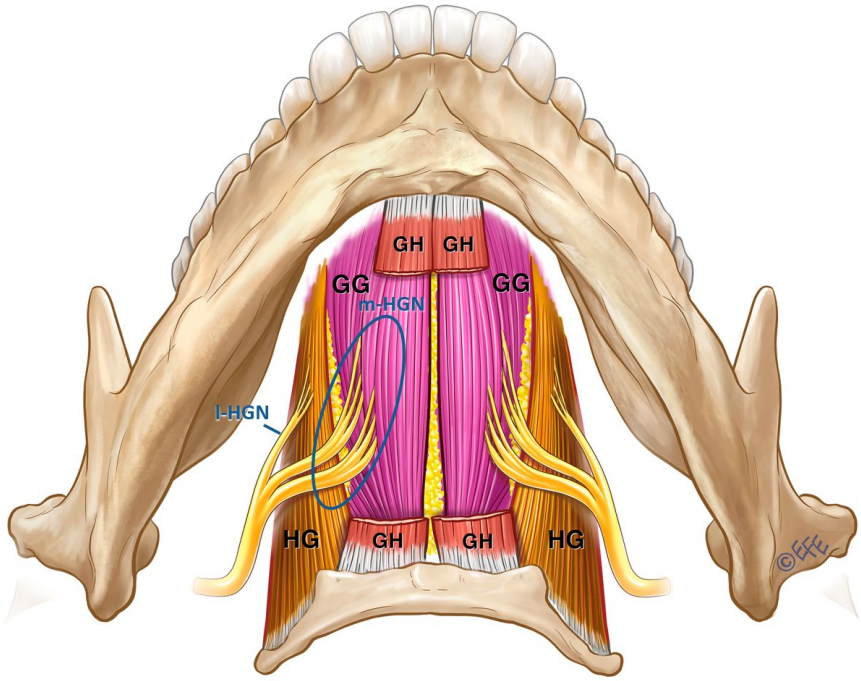


Figure 17: Identification of the medial (m-HGN) and lateral (l-HGN) branches of the hypoglossal nerve. GG = Genioglossus. HG = Hyoglossus/ GH = Geniohyoid.

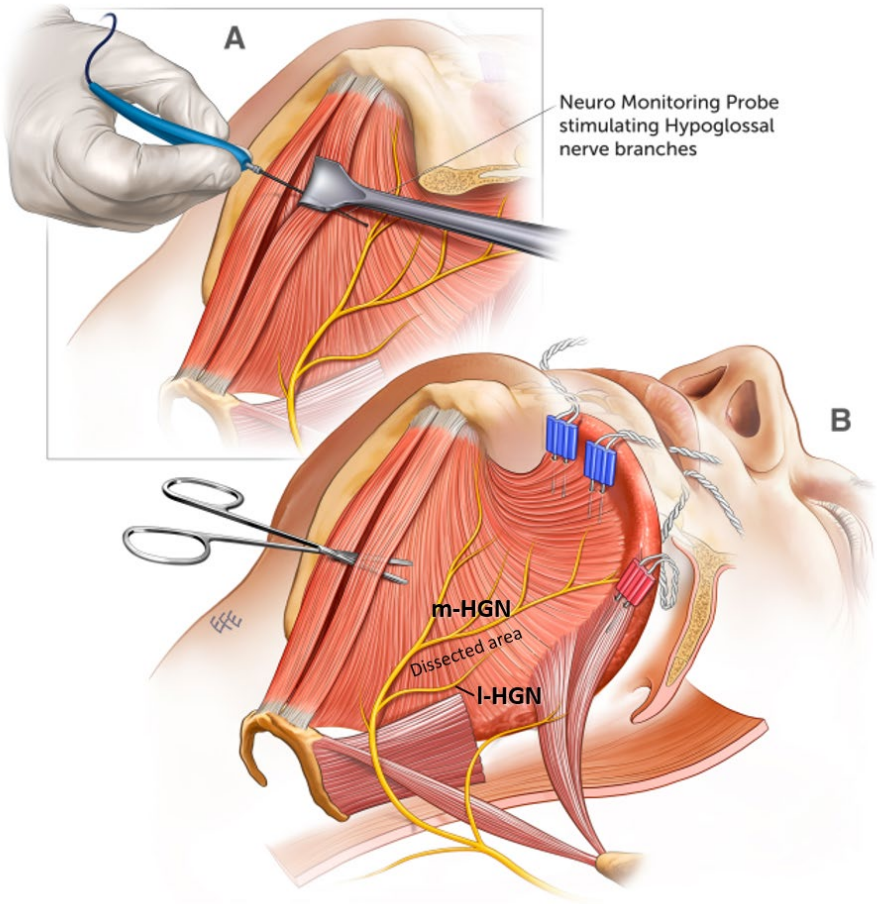


Figure 18: Exposure of left hypoglossal nerve branches and neuro monitoring testing

5.4.4 Implantable Stimulator Placement

- Take the Implantable Stimulator Kit. Verify the expiration date and package integrity.
- Open the double blister package. The package is comprised of two inner blisters, containing the Implantable Stimulator and the Surgical Template.

WARNING: Do not use the devices if the Implantable Stimulator, Surgical Template or package is kinked, damaged or past its expiration date.

5.4.4.1 Optional Use of Surgical Template

- Identify the Surgical Template inner blister and open it.
- Use the Surgical Template to assist you in creating enough space to accommodate the Implantable Stimulator paddles (see Figure 19).
- Once inserted, the electrode windows of the Surgical Template can be used to visualize the underlying nerve branches, ensuring the Implantable Stimulator electrodes will face the inclusionary branches of the hypoglossal nerve (see Figure 20).
- Further validation can be conducted by stimulating the selected branches using the neuromonitoring probe through the Surgical Template electrodes windows (see Figure 20).
- Once paddle areas have been established, remove the Surgical Template from the implantation site.

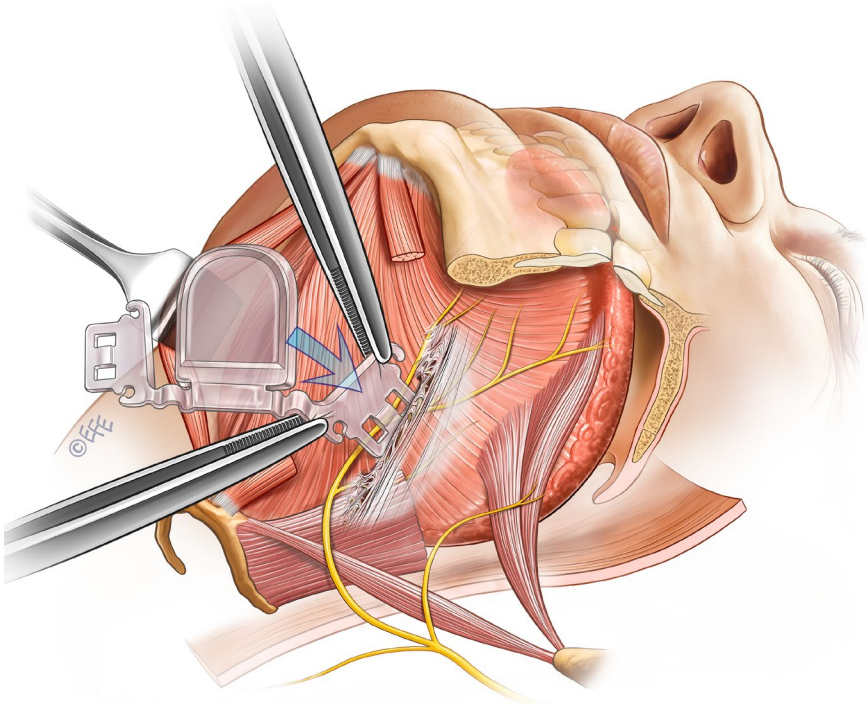


Figure 19: Sizing of the dissection area using the Surgical Template

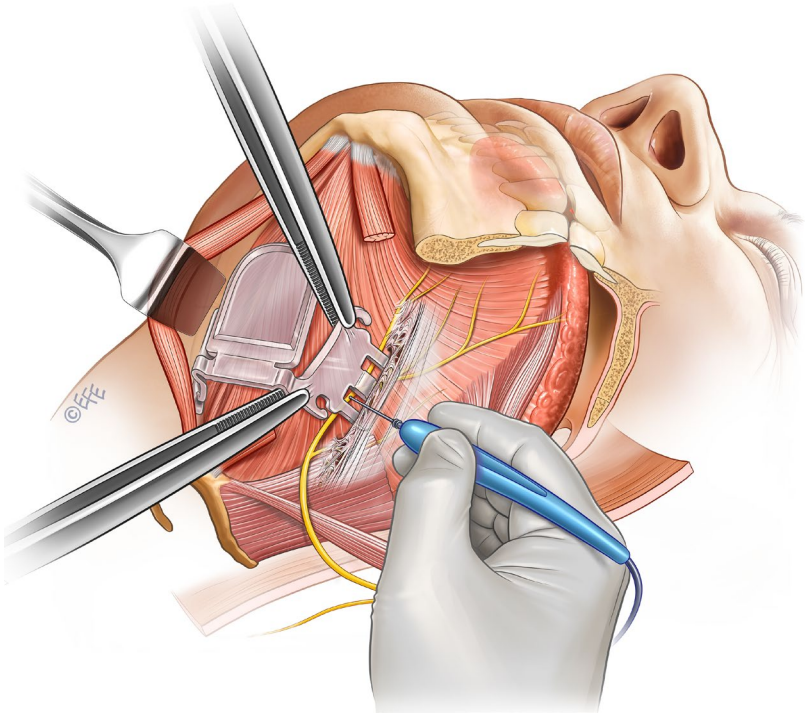


Figure 20: Verification of HGN branches selection via IONM stimulation through the Surgical Template electrodes windows

5.4.4.2 Implantable Stimulator Placement Procedure

- Identify the Implantable Stimulator inner blister and open it. Visually inspect the implant to verify there is no kinking or damage.

CAUTION: Avoid significant tilting of the open inner blister to prevent accidental fall of the Implantable Stimulator.

CAUTION: Handle implant with care: do not use sharp instruments to handle the Implantable Stimulator and avoid touching the electrodes area.

- Position the implant flat on the genioglossus muscle with each paddle positioned in the dissected paddle areas. The two electrodes (see Figure 21) on each paddle should face the terminal fibers of the hypoglossal nerve medial branch. The ceramic housing portion of the implant should face the anterior part of the chin, without touching the mandible (see Figure 22).

NOTE: If the chin anatomy does not allow for successful placement of the Implantable Stimulator, it should not be implanted.

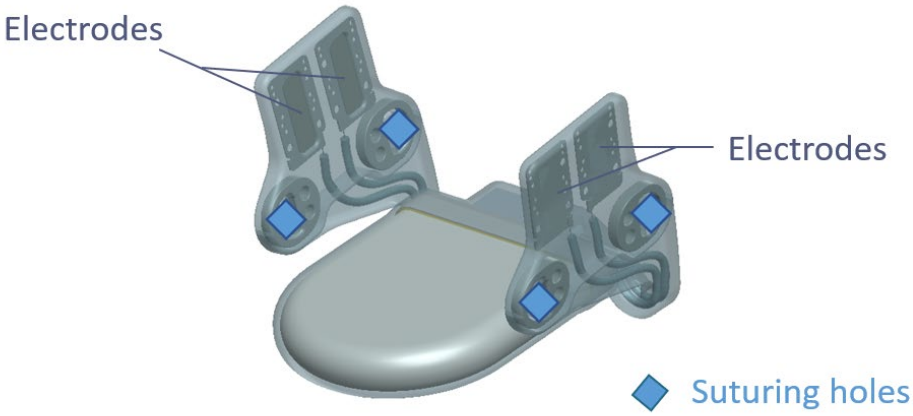


Figure 21: Four electrodes and four suturing holes of the implant

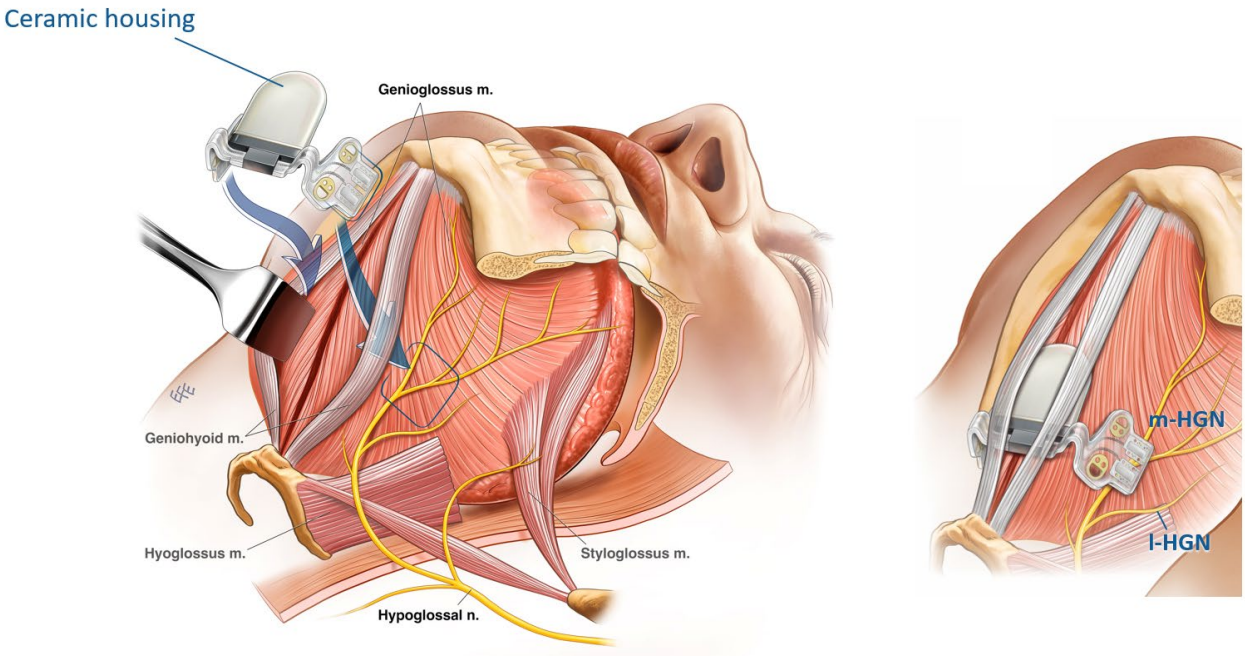


Figure 22: Implant placement over the Genioglossus muscle

5.4.5 Implantable Stimulator Suturing

After the Implantable Stimulator is in the targeted location, the implant should be secured to the genioglossus muscle through the 4 dedicated suturing holes (refer to Figure 21 above and Figure 23 below) using non-absorbable braided 2-0 sutures.

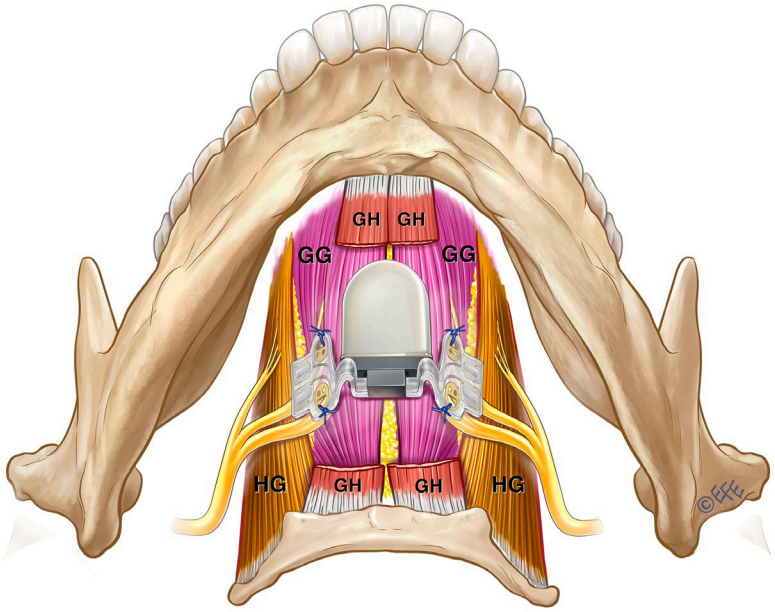


Figure 23: Sutured Implantable Stimulator

WARNING: Suturing near nerve branches and blood vessels may cause damage, ensure optimal visibility of surgical area during fixation of the implant.

WARNING: Puncturing the implant will cause implant malfunction either immediately or later. Use caution when suturing the device and ensure needle only enters the dedicated suture holes. In case of puncture, replace the implant immediately.

5.4.6 External Stimulator Test

The External Stimulator is used to verify Implantable Stimulator functionality and device placement according to the instructions below:

- Verify package integrity and expiration date on the External Stimulator box.
- Retrieve the External Stimulator from sterile package. Visually inspect the device to verify there is no damage or kinking.

WARNING: Do not use the device if the External Stimulator or package is kinked, damaged, or past its expiration date.

WARNING: To ensure optimal performance of the External Stimulator, verify the External Stimulator is not used in close proximity to large metallic surfaces (including large metal retractors).

- Using the latch mechanism, **fully retract** the External Stimulator antenna.
- Retract the muscle layers to expose the Implantable Stimulator ceramic housing.
- Position the External Stimulator flat tip flush and concentric (direct contact and alignment) with the Implantable Stimulator ceramic housing without applying pressure to the Implantable Stimulator (see Figure 24).
- Remove the metal retractors.
- Press the power button of the External Stimulator; the External Stimulator LED displays orange when turned on and stimulation pulses are delivered to the implant.
- Adjust the stimulation intensity by sliding the External Stimulator antenna up or down to confirm appropriate stimulation response.

NOTE: An appropriate stimulation response is symmetric protrusion of the tongue at least past the lower incisors with no obvious retraction or twisting of the tongue.

- Press the External Stimulator power button to turn it OFF.
- If necessary, reposition the Implantable Stimulator paddles and repeat these steps until appropriate stimulation response is observed.

NOTE: An appropriate stimulation response is symmetric protrusion of the tongue at least past the lower incisors with no obvious retraction or twisting of the tongue.

NOTE: The External Stimulator turns off automatically after five minutes of operation.

CAUTION: Do not use External Stimulator retraction mechanism without pressing the button. The External Stimulator should be turned off while not in use. The External Stimulator operation time is limited to 60 minutes.

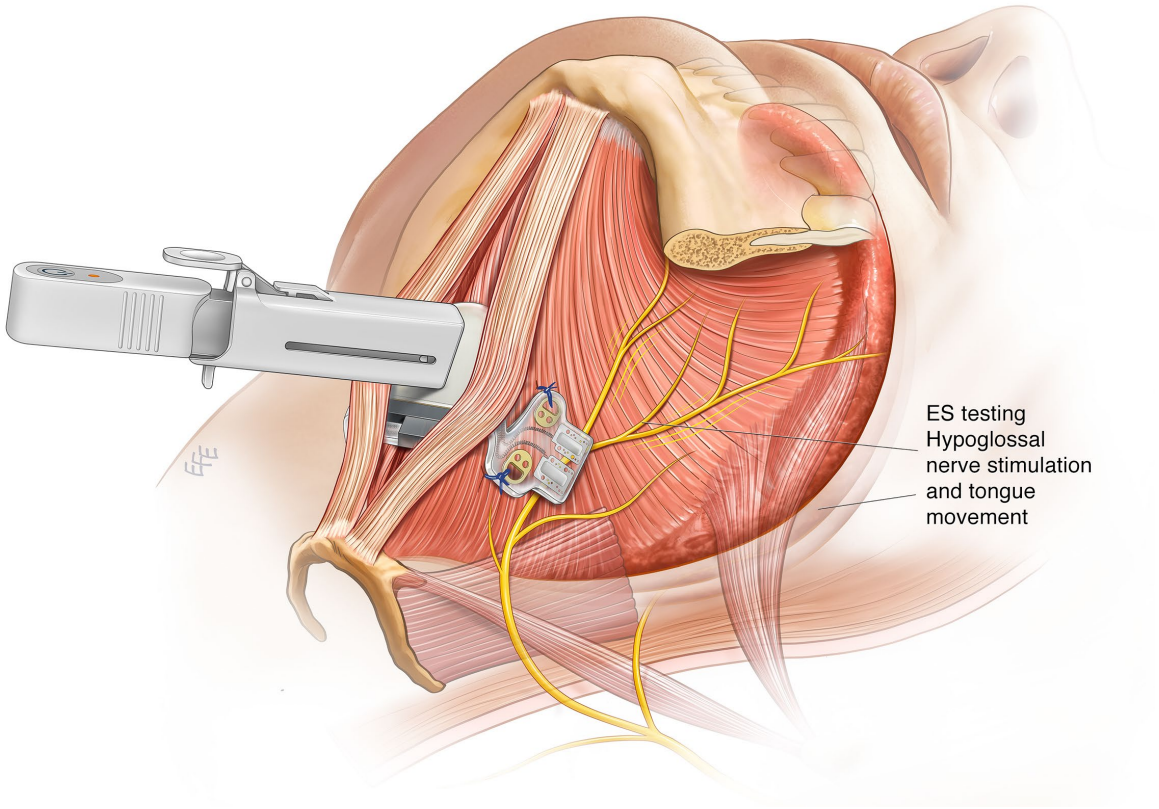


Figure 24: Implant location verification with the External Stimulator

5.4.7 AC/DP Test prior to Skin Closure

Remove all the retractors and partially close the skin with a single temporary suture to confirm the Implantable Stimulator placement using the AC/DP as per the instructions below:

- Nyxoah field staff will reset the Activation Chip in the Charging Unit and connect the Activation Chip onto a new Disposable Patch.
- Nyxoah field staff will program the Activation Chip using the following stimulation parameters:
    - Stimulation mode: LAB
    - Pulse Frequency: 35 Hz
    - Pulse Duration: 120 µsec
    - Stimulation Amplitude: 1%
    - Train length: 2 sec
    - Train interval: 2 sec
- Nyxoah field staff will turn ON the Activation Chip LED to visualize when the stimulation is ON.
- Place the AC/DP combination into a sterile sleeve or equivalent. Visually inspect the sleeve to confirm the sterile barrier is intact after the AC/DP has been inserted.

WARNING: Breach of the sterile barrier during insertion of the AC/DP poses a potential infection risk to the patient. The AC/DP should only be placed on the patient after the integrity of the sterile sleeve has been confirmed to be fully intact.

- Place the AC/DP over the surgical incision, positioning the Disposable Patch flush with the skin and with the Disposable Patch antenna above the Implantable Stimulator antenna (see Figure 25).
- Check stimulation response by observing both neuro monitoring signals and anatomical tongue response.
- Nyxoah field staff will adjust pulse duration and/or amplitude until appropriate anatomical response is achieved.

If appropriate stimulation response is not achieved or if amplitudes greater than 20% are required to achieve an appropriate response, reposition the Implantable Stimulator and repeat steps 5.4.6 and 5.4.7 as necessary.

NOTE: An appropriate stimulation response is symmetric protrusion of the tongue at least past the lower incisors with no obvious retraction or twisting of the tongue.

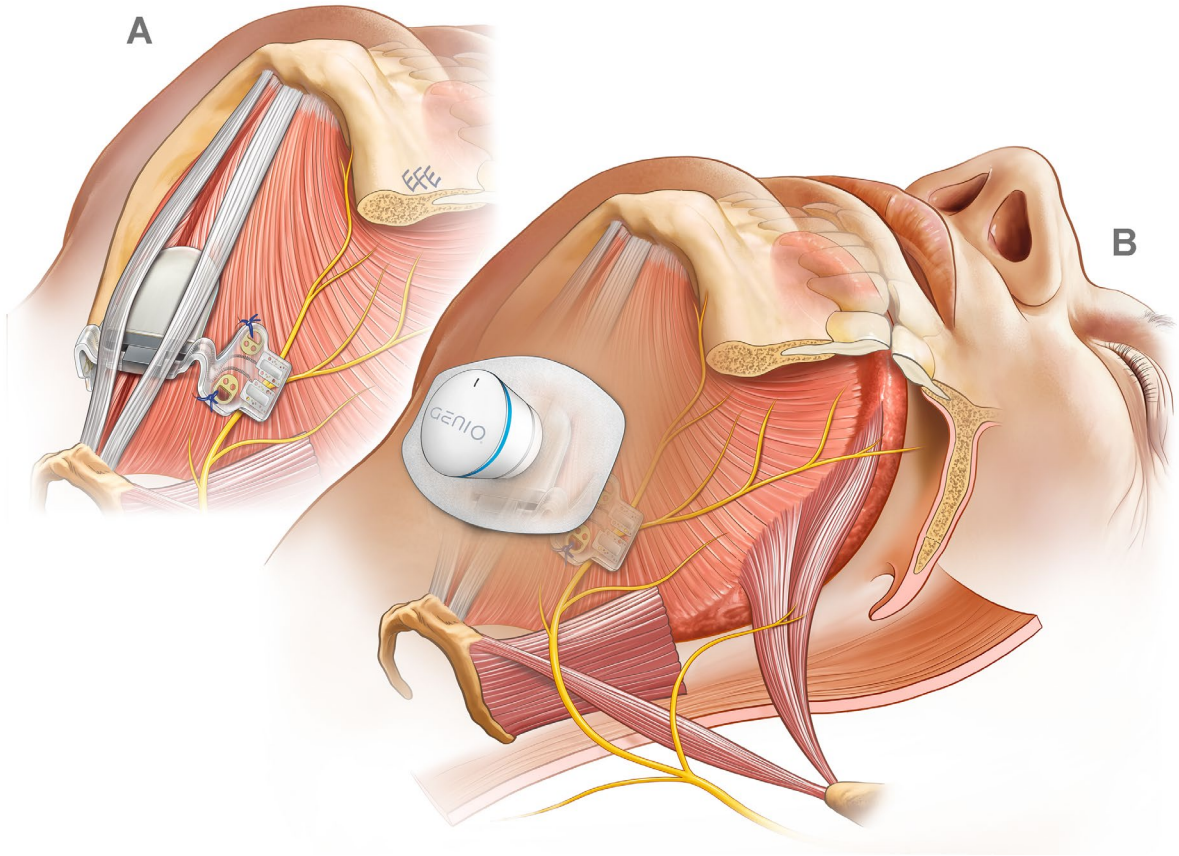


Figure 25: Implant testing with AC/DP combination[3]

[3] Note that this picture does not show the sterile sleeve/bag and is for reference only.

5.4.8 Implantable Stimulator to Skin Distance Measurement

Measure the distance between the skin and the Implantable Stimulator ceramic housing and verify it is less than 3 cm. **If the distance is greater, it may cause the implant not to respond to activation post-surgery or may require higher stimulation amplitude.** The surgeon may, at their own discretion, perform standard lipectomy techniques to reduce the size of the subcutaneous fat layer, ensuring the distance is no less than 2 cm.

5.4.9 Skin Closure

Once the implant is sutured and proper stimulation response is achieved, close the surgical incision (see Figure 26).

Closure of the surgical site should be performed in layers using absorbable sutures in the deep layers and either absorbable or removable sutures in the skin.

NOTE: If non-absorbable sutures are used for skin closure, include suture removal post-operative instructions to the patient.

WARNING: Staples should not be used for skin closure as they have not been evaluated for use with the AC/DP after skin closure.

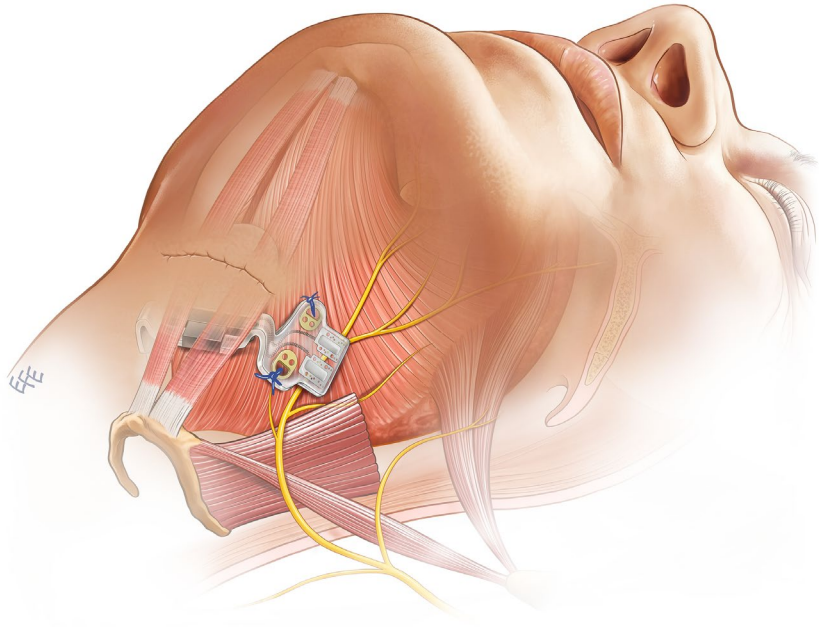


Figure 26: Skin closure

5.4.10 Final AC/DP Test after Skin Closure

Once the surgical incision closed, conduct a final AC/DP test to confirm proper Implantable Stimulator placement and stimulation response (see AC/DP instructions in section 5.4.7).

If appropriate stimulation response is not achieved or if amplitudes greater than 20% are required to achieve an appropriate response, reopen the surgical incision, reposition the Implantable Stimulator and repeat steps 5.4.6 and 5.4.7 as necessary.

NOTE: An appropriate stimulation response is symmetric protrusion of the tongue at least past the lower incisors with no obvious retraction or twisting of the tongue.

WARNING: Do not implant if at the end of the implant procedure, the patient shows sub-optimal response to stimulation.

5.4.11 Devices Disposal

Once the surgery is completed:

- The used External Stimulator(s) and Surgical Templates are considered biohazard waste and must be disposed of using the hospital biohazard containers. Proper method of potential biohazard Disposal of the medical device equipment shall be done per local laws and regulations.
- Inspect the Activation Chip and the sterile sleeve/camera bag used for the AC/DP tests. If the sterile sleeve/camera bag appears intact, and the Activation Chip appears to be free of fluid/debris, return the Activation Chip to its box for storage. Dispose of the used Disposable Patch(s).

WARNING: If during inspection of the Activation Chip and sterile sleeve/camera bag, the integrity of the sterile barrier is found to be compromised, or the Activation Chip appears to be soiled, dispose of the Activation Chip using the hospital biohazard containers.

- Opened Implantable Stimulator(s) should be returned to Nyxoah.

6 Implantable Stimulator Explant and Revision Procedures

6.1 Overview of the Procedures

Before beginning the explant/revision procedure, become familiar with all the equipment involved in this surgical procedure. Only certified surgeons who completed training by Nyxoah can perform the surgical procedures of the Implantable Stimulator.

Patients can elect to have their Implantable Stimulator explanted.

A revision procedure has three possible outcomes: repositioning, replacement (removal with a new Implantable Stimulator implanted), and explant (removal with no replacement of Implantable Stimulator). The decision to reposition, replace or explant the Implantable Stimulator will be made by the surgeon, and is dependent upon the condition of the Implantable Stimulator and/or the anatomy of each patient, as described below:

- Repositioning: if upon reaching the implantation site no visible damage to the Implantable Stimulator components is observed and testing with the External Stimulator and AC/DP verifies that the implant functionality remains intact, one or both of the Implantable Stimulator electrodes may be repositioned to capture the inclusionary branches of the HGN,
- Replacement: if upon reaching the implantation site there is visible damage to the implant or functionality of the implant is compromised, the Implantable Stimulator will be explanted and the surgeon will implant a new Implantable Stimulator,
- Explant: if repositioning or replacement are not possible due to the patient's anatomy, the Implantable Stimulator will be permanently explanted.

NOTE: At any point during a revision (repositioning or replacement) surgery, the surgeon can opt to abort the procedure. This decision should be based on the surgeon's medical judgement and could include the following scenarios:

- The surgeon believes the patient is at risk for nerve injury or additional complications with further surgery
- The surgeon does not feel that an appropriate therapeutic response will be achieved with the implant (e.g., unable to get appropriate anatomical response during the revision procedure).

6.2 Surgical Materials

Refer to Section 5.2 as applicable).

6.3 Preparation and Positioning

Refer to Section 5.3.

6.4 Implantable Stimulator Explant/Revision/Replacement

6.4.1 Skin Incision

Refer to Section 5.4.1 or utilize prior incision scar if visible.

6.4.2 Reaching Implantation Site

Following skin incision, dissect down to previously implanted Implantable Stimulator as per Section 5.4.2.

NOTE: If scar tissue formation from prior Implantable Stimulator implantation prevents discerning the different muscle layers, a midline dissection through the mylohyoid and geniohyoid muscles down to the implant should be performed.

6.4.3 Implantable Stimulator Repositioning

- Expose previously implanted Implantable Stimulator.
- Reposition the Implantable Stimulator as necessary, suture and test according to Sections 5.4.4 to 5.4.10.

NOTE: Standard prophylactic techniques should be employed.

WARNING: Do not implant if at the end of the repositioning procedure, the patient shows sub-optimal response to stimulation.

6.4.4 Implantable Stimulator Explant

- Expose previously implanted Implantable Stimulator.
- Remove existing sutures and explant Implantable Stimulator while maintaining integrity of the explanted Implantable Stimulator as best as possible.
- Close the surgical incision per Section 5.4.9.

6.4.5 Implantable Stimulator Replacement

In case of a replacement procedure, following previously implanted Implantable Stimulator explant, refer to Sections 5.4.4 to 5.4.10 for new Implantable Stimulator placement, testing and suturing.

NOTE: Standard prophylactic techniques should be employed.

WARNING: Do not implant if at the end of the replacement procedure, the patient shows sub-optimal response to stimulation.

6.4.6 Skin Closure

Refer to Section 5.4.9.

6.4.7 Devices Disposal

Refer to Section 5.4.11 (as applicable).

Return all explanted components to Nyxoah.

7 Postoperative Follow-Up

A postoperative check should be performed between 4-10 days by the Surgeon or their surrogate to check the patient's well-being and examine the wound for swelling, erythema, discharge, bleeding or breakdown. In case an implantation, revision or replacement surgery was performed, the implant should not be activated for eight (8) weeks following surgery to allow proper healing.

8 Health Care Provider Instructions to Patient

Patients should be instructed:

- That it is normal to feel some discomfort at the implantation site.
- To monitor their wound for bleeding, excessive swelling, redness, and report shortness of breath, swallowing difficulties, fever > 101°F and excessive pain not being controlled with prescribed analgesics.
- Patients who are capable and willing to use PAP should be advised to continue use until device activation. Those who are unable or unwilling to use PAP have likely not been receiving any treatment for their OSA and should continue usual care for their OSA until device activation.
- That if they have any concerns, they should contact their health care provider.
- To avoid physical activities that could damage the implant site or implanted device:
    - Avoid any activities that involve manipulation or force to the neck as this may damage or displace your Genio® Implantable Stimulator such as jack-hammering, mixed martial arts, Brazilian jiu-jitsu, wrestling, extreme sports, etc.
    - Avoid any activities that could have significant stress on the neck such as diving, boxing, bumper cars etc.
    - The impact of pressure changes which could be encountered during scuba diving have not been evaluated and this activity should be avoided.
- To inform their personal and consulting health care providers or dentists as to the presence and nature of their implant and to refer them to the implant card for additional information about the implant.
- To carry their implant card all the time.

9 Patient Monitoring

Healthcare providers should adhere to current standard of care clinical practice for the long-term management of patients with OSA, including regular patient follow-up visits to assess treatment response, device function, and patient safety, as well as repeat sleep testing when clinically indicated to evaluate ongoing treatment effectiveness.

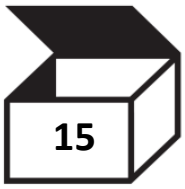
10 Symbols on Product or Package Labeling

Symbol/Title	Explanatory Text	Standard/Reference Number
 Manufacturer	Indicates the manufacturer of the medical device	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.1] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [3082]
 Catalogue number	Indicates the manufacturer's catalogue number so that the medical device can be identified	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.6] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2493]
 Serial number	Indicates the serial number of the medical device to allow for identification	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.7] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2498]
 Batch code	Indicates the batch code so that the batch or the lot of the medical device can be identified. Other synonyms for "batch code" are "lot number", "lot code" and "batch number"	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.5] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2492]
 Date of manufacture	Indicates the date when the medical device was manufactured	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.3] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2497]

Symbol/Title	Explanatory Text	Standard/Reference Number
 Use-by date	Indicates the date after which the medical device is not to be used. Other synonyms for "use-by date" are "use by", "expiry date" and "expiration date"	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.4] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2607]
 Follow instructions for use	Indicates that reading the instruction manual prior to operating the device is mandatory	IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.2, Symbol 10] ISO 7010:2019 – Graphical symbols – Safety colours and safety signs – Registered safety signs [M002]
 Caution	Indicates that caution is necessary when operating the device or control close to where the symbol is placed, or that the current situation needs operator awareness or operator action in order to avoid undesirable consequences	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.4.4] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [0434A]
 Sterilized using ethylene oxide	Indicates that the medical device has been sterilized using ethylene oxide	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.2.3] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2501]
 Do not use if package is damaged and consult instructions for use	Indicates that the medical device should not be used if the package has been damaged or opened and that the user should consult the instructions for use for additional information	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.2.8] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2606]

Symbol/Title	Explanatory Text	Standard/Reference Number
 Do not resterilize	Indicates that the medical device is not to be resterilized	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.2.6] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2608]
 Do not re-use	Indicates that the medical device is intended for one single use only	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.4.2] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [1051]
 Keep away from sunlight	Indicates that the medical device needs protection from light sources	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.3.2] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [0621]
 Keep dry	Indicates that the medical device needs to be protected from moisture	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.3.4] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [0626]
 Temperature limit	Indicates the temperature limits to which the medical device can be safely exposed	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.3.7] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [0632]
 Humidity limitation	Indicates the range of humidity to which the medical device can be safely exposed	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.3.8] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2620]

Symbol/Title	Explanatory Text	Standard/Reference Number
 Magnetic Resonance (MR) Conditional	Indicates an item with demonstrated safety in the MR environment within defined conditions including conditions for the static magnetic field, the time-varying gradient magnetic fields and the radiofrequency fields	ASTM F2503-20 – Standard Practice For Marking Medical Devices And Other Items for Safety In The Magnetic Resonance Environment [3.1.11]
 Prescription Use Only	Indicates that Federal (USA) law restricts the device to sale by or on the order of a licensed physician	United States Code of Federal Regulations; 21 CFR 801.109(b)(1)
 Class II Equipment	Identifies equipment which meets the safety requirements specified for Class II equipment (double insulated equipment)	IEC 60417:2002 – Graphical symbols for use on equipment [5172] IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.1, Symbol 9]
 Non-ionizing electromagnetic radiation	Indicates medical electrical equipment that includes RF transmitters or that intentionally apply RF electromagnetic energy for diagnosis or treatment	IEC 60417:2002 – Graphical symbols for use on equipment [5140]
 Type BF applied part	Identifies a type BF applied part (a part which is generally not conductive and can be immediately released from the patient)	IEC 60417:2002 – Graphical symbols for use on equipment [5333] IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.1, 20]
 FCC Mark	Indicates that the electromagnetic radiation of the device is below the limits specified by the Federal Communications Commission	United States Code of Federal Regulations; Title 47

Symbol/Title	Explanatory Text	Standard/Reference Number
IP21 Degrees of protection provided by enclosures	Indicates that the device is protected against the ingress of solid objects over 12.5mm and protected against ingress of vertically dripping water	IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.3, Symbol 2]
IP22 Degrees of protection provided by enclosures	Indicates that the device is protected against the ingress of solid objects over 12.5mm and protected against ingress of dripping water at any angle up to 15 degrees from vertical	IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.3, Symbol 2]
 Quantity in box	Indicates the amount of devices contained within the box	ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2794]
 Unique device identifier	Indicates a carrier that contains unique device identifier information	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.7.10]
 Waste electrical and electronic equipment	Indicates that the disposal of the device requires separate collection in the European Union	Directive 2012/19/EU on waste electrical and electronic equipment (WEEE)
 Sterile Barrier System	Indicates a single sterile barrier system with protective packaging inside	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.2.13] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [3708]

11 EMC Requirements – Genio® System 2.1

11.1 Use Environment

The following Genio® System 2.1 components are used by the surgeon in an Operating Room environment:

- Genio® Implantable Stimulator Model #2954
- Genio® External Stimulator
- Genio® Activation Chip
- Genio® Disposable Patch
- Genio® Charging Unit

11.2 Essential Performance

The following table lists the aforementioned devices' essential performance functions per system component:

Device	Essential performance functions
Implantable Stimulator Model #2954	Delivering stimulation pulses according to 8MHz electromagnetic field transmitted from an external device (AC or ES)
External Stimulator	Transmission of 8MHz EM field to power the Implantable Stimulator
Activation Chip and Disposable Patch	Transmission of modulated 8 MHz EM field to power the Implantable Stimulator
Charging Unit and Power Supply	Charging Activation Chip battery

11.3 Medical Device wireless functions

Device	Intended use environment	Specific RF wireless type	Type	Wireless functions
Implantable Stimulator Model #2954	Sleep lab, Surgery Operation Room and Home use	Wireless modulated energy transfer 8 MHz	Receiver	Receiving stimulation energy and pattern from External Stimulator or AC/DP
External Stimulator	Surgery Operation Room	Wireless modulated energy transfer 8 MHz	Transmitter	Energy transfer to Implantable Stimulator

Device	Intended use environment	Specific RF wireless type	Type	Wireless functions
Activation Chip/Disposable Patch	Sleep lab, Surgery Operation Room and Home use	Wireless modulated energy transfer 8 MHz	Transmitter	Energy transfer to Implantable Stimulator
		BLE (Bluetooth Low Energy) 2.4 GHz	Transceiver	Communication

11.4 EMC Warnings

WARNING: 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.

WARNING: 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.

WARNING: Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the Genio® System 2.1, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.

WARNING: The Genio® System 2.1 needs special precautions regarding EMC and needs to be installed and put into service according to the specific instructions for maintaining basic safety and essential performance with regard to electromagnetic disturbances for the expected service life provided in sections 2.4 and 2.6.

11.5 Power Inputs and Frequencies

The following table lists the Genio® System 2.1 devices power inputs and Radio frequencies (if applicable):

Device	Power Inputs	Radio Frequencies
External Stimulator	3.7V, 120mAh (Battery Powered)	8MHz
Activation Chip/Disposable Patch	4.2 V, 160 mAh (Battery Powered)	8 MHz BLE: 2.4 GHz
Charging Unit	110-240 V, AC 50-60 Hz	N/A

11.6 EMC Guidance Tables

11.6.1 Guidance and MANUFACTURER'S declaration – ELECTROMAGNETIC EMISSIONS IEC 60601-1-2 Ed.4

Emissions test	Compliance	Electromagnetic environment - guidance
RF emissions CISPR 11	Group 1	The Genio® System 2.1 uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment
RF emissions CISPR 11	Class B	The Genio® System 2.1 is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.
Harmonic emissions IEC 61000-3-2	Class A	
Voltage fluctuations/flicker emissions IEC 61000-3-3	Complies	

11.6.2 Guidance and manufacturer's declaration – electromagnetic IMMUNITY IEC 60601-1-2 Ed.4

Immunity test	IEC 60601 level	Compliance level	Electromagnetic environment - guidance
Electrostatic discharge (ESD), IEC 61000-4-2	8 kV contact 15 kV air	8 kV contact 15 kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30 %.
Electrical fast transient/burst, IEC 61000-4-4	2 kV for power supply lines 1 kV for SIP/SOP lines	2 kV for power supply lines 1kV for SIP/SOP lines	Mains power quality should be that of a typical commercial or hospital environment
Surge, IEC 61000-4-5	1 kV line to line 2 kV line to earth	1 kV line to line (class II ME equipment and ME systems according to Table 5, Note "k" of EN/IEC 60601-1-2)	Mains power quality should be that of a typical commercial or hospital environment.
Voltage dips and interruptions on power supply input lines IEC 61000-4-11	0 % U_T for 0,5 cycle 0 % U_T for 1 cycle 70 % U_T for 25/30 cycles 0 % U_T for 250/300 cycles	0 % U_T for 0,5 cycle 0 % U_T for 1 cycle 70 % U_T for 25/30 cycles 0 % U_T for 250/300 cycles	Mains power quality should be that of a typical commercial or hospital environment. If the user of the equipment requires continued operation during power mains interruptions, it is recommended that the equipment be powered from an uninterruptible power supply or a battery.
Power frequency magnetic field, IEC 61000-4-8	30 A/m	30 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
NOTE: U_T is the AC mains voltage prior to application of the test level.			

11.6.3 Guidance and manufacturer's declaration – electromagnetic IMMUNITY IEC 60601-1-2 Ed.4.1

Immunity test	IEC 60601 level	Compliance level
IEC 61000-4-6 Conducted RF	3 Vrms 150 kHz to 80 MHz 6 Vrms in ISM bands (6.765 MHz to 6.795 MHz; 13.553 MHz to 13.567 MHz; 26.957 MHz to 27.283 MHz; and 40.66 MHz to 40.70 MHz) and amateur radio bands (1.8 MHz to 2.0 MHz, 3.5 MHz to 4.0 MHz, 5.3 MHz to 5.4 MHz, 7 MHz to 7.3 MHz, 10.1 MHz to 10.15 MHz, 14 MHz to 14.2 MHz, 18.07 MHz to 18.17 MHz, 21.0 MHz to 21.4 MHz, 24.89 MHz to 24.99 MHz, 28.0 MHz to 29.7 MHz and 50.0 MHz to 54.0 MHz)	[*V*] = 3 Vrms [*V*] = 6 Vrms
IEC 61000-4-3 Radiated RF	AC, DP, IS, PS, CU parts of Genio® System 10 V/m 80 MHz to 2.7 GHz ES parts of Genio® System 3 V/m 80 MHz to 2.7 GHz	[*E*] = 10 V/m
Proximity fields from RF wireless communications equipment	385 MHz	27 V/m
	450 MHz	28 V/m
	710 MHz	9 V/m
	745 MHz	
	780 MHz	
	810 MHz	28 V/m
	870 MHz	
	930 MHz	
	1720 MHz	28 V/m
	1845 MHz	
	1970 MHz	
	2450 MHz	28 V/m
	5240 MHz	9 V/m
	5500 MHz	
	5785 MHz	

11.6.4 RF Receivers and Transmitters Specifications

RF	Tx/Rx	Frequency, MHz	Assigned Frequency Range, MHz	Modulation	EIRP / Transmitter Power
Bluetooth	Tx/Rx	2400 [2402-2480]	2400-2483.5	GFSK	EIRP: -14.20 dBm (38 µW)
Power Transfer (External Stimulator)	Tx	8 [7.985-8.01125]	7.4-8.8	Per Treatment Protocol	H-Field strength: -2.88 dB(µA/m)
Power Transfer (Activation Chip/Disposable Patch)	Tx	8 [7.985-8.01125]	7.4-8.8	Per Treatment Protocol	H-Field strength: 34.7 dB (µA/m) (54.3 µA)

Note – applicable for devices used in the operating room.