Inspire®

System Implant Manual

[#] 3150 Generator
[#] 4063 Stimulation Lead

Rx ONLY

Table of Contents

Explanation of Symbols on Product or Package Labeling

Symbol	Title	Description	Standard Reference
	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; ISO 7000-0434A
	Consult instructions for use or electronic instructions for use	Indicates the need for the user to consult the instructions for use	ISO 15223-1; ISO 7000-1641
	Manufacturer	Indicates the medical device manufacturer	ISO 15223-1; ISO 7000-3082
	Date of manufacture	Indicates the date when the medical device was manufactured	ISO 15223-1; ISO 7000-2497
	Country of manufacture	To identify the country of manufacture. The “CC” shall be replaced by the two-letter country code	ISO 15223-1; ISO 60417-6049
	Do not reuse	Indicates a medical device that is intended for one single use only	ISO 15223-1; ISO 7000-1051
	Do not resterilize	Indicates a medical device that is not to be resterilized	ISO 15223-1; ISO 7000-2608
	Medical device	Indicates the item is a medical device	ISO 15223-1
	Catalog number	Indicates the manufacturer’s catalog number so that the medical device can be identified	ISO 15223-1; ISO 7000-2493
	Serial number	Indicates the manufacturer’s serial number so that a specific medical device can be identified	ISO 15223-1; ISO 7000-2498
	Model number	Indicates the model number or type number of a product	ISO 15223-1; IEC 60417-6050

Symbol	Title	Description	Standard Reference
	Unique device identifier	Indicates a carrier that contains unique device identifier information	ISO 15223-1
	Use by date	Indicates the date after which the medical device is not to be used	ISO 15223-1; ISO 7000-2497
	Temperature limitation	Indicates the temperature limits to which the medical device can be safely exposed	ISO 15223-1; ISO 7000-0533
	Do not use if package is damaged	Indicates that a medical device that 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; ISO 7000-2606
	Sterilized using ethylene-oxide gas with a double sterile barrier system	Indicates two sterile barrier systems that have been sterilized using ethylene oxide	ISO 15223-1; ISO 7000-2501 & ISO 7000-3704
	Sterilized using ethylene oxide with a single sterile barrier and protective packaging inside	Indicates a single sterile barrier that has been sterilized using ethylene oxide system with protective packaging inside	ISO 15223-1; ISO 7000-2501 & ISO 7000-3708
	Sterilized using ethylene oxide	Indicates a medical device that has been sterilized using ethylene oxide	ISO 15223-1; ISO 7000-2501
	Patient information website	Indicates a website where a patient can obtain additional information on the medical product	ISO 15223-1; ISO 7000-3705
	Date of implant	Indicates the date that information was entered or a medical procedure took place	ISO 15223-1; ISO 7000-5662
	Patient identification	Indicates the identification data of the patient	ISO 15223-1; IEC 60417-5664
	Health care center or doctor	Indicates the address of the health care center or doctor where medical information about the patient may be found	ISO 15223-1; ISO 7001

Symbol	Title	Description	Standard Reference
	Packaging unit/quantity	Indicates the number of pieces in the package	IEC 60417; ISO 7000-2794
	Peel/open here	Identifies the location where the package can be opened and to indicate the method of opening it.	IEC 60417; ISO 7000-3079
	MR Conditional	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
Rx ONLY	Federal (USA) law restricts this device to sale by or on the order of a physician	Indicates that Federal (USA) law restricts this device to sale by or on the order of a physician	CFR Title 21

Overview of the Manual

This manual provides physicians with implant procedure and follow-up care information for the Inspire system. The manual includes instructions for handling, storing, and implanting the leads and the generator. Critical therapy information is provided for you to discuss with your patient, as well as instructions for follow-up care. The generator and lead cannot be resterilized. Information on explanting the generator and the lead is included. This manual also explains how to register your patient's medical devices.

Sales Package Contents

The lead and generator are provided in separate sterile packages.

Inspire 3150 Generator

- Sterile package contents
  - One generator
  - One torque limiting hex wrench
- Product literature (patient manual, patient registration form, patient implant card, and electronic labeling insert)
  NOTE: The system implant manual is provided at manuals.inspiresleep.com.

Inspire 4063 Stimulation Lead

- Sterile package contents
  - One stimulation lead
  - One tunneling tool
- Electronic labeling insert
  NOTE: The lead manual is provided at manuals.inspiresleep.com.

Implanted Component Descriptions

The implanted components of the Inspire system consist of a generator and a stimulation lead. All implanted Inspire system components are intended for single-use only.

Generator

The generator (Figure 1) contains the battery and electronics that deliver Inspire therapy, sense inspiration, and store the therapy settings.

Figure 1. *Generator*

The generator has a 3.2 mm low-profile connector port (Figure 2), which is compatible with the connector on the stimulation lead. After inserting the lead connector into the generator connector port, the lead connector is secured using the set screw next to the connector port.

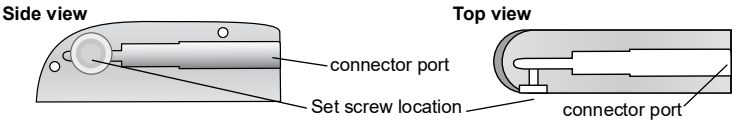


Figure 2. *Generator connector port*

The stimulation lead

The stimulation lead (Figure 3) delivers stimulation to the hypoglossal nerve. The lead has a flexible, self-sizing stimulation cuff. The stimulating electrodes are on the inner surface of the cuff.

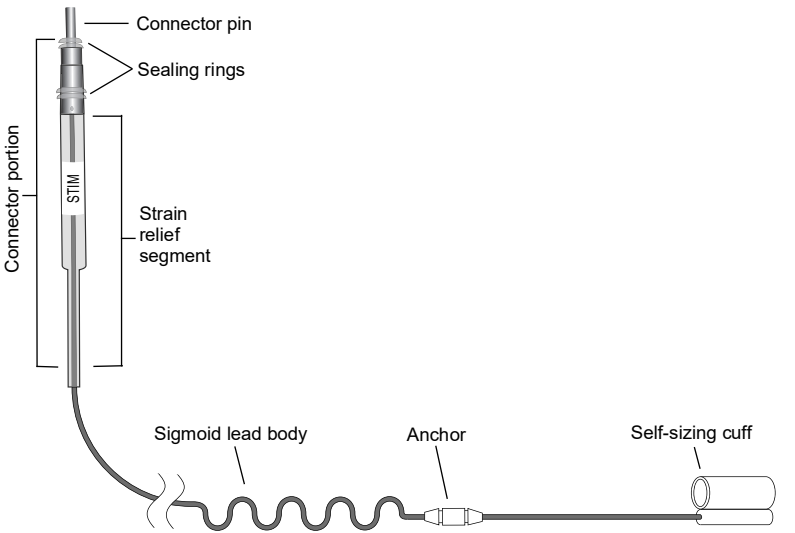


Figure 3. *Stimulation lead*

Device Compatibility

- Program the Inspire 3150 Generator with the Inspire 2740S Programmer and the Inspire 2740C Programmer Cable.

Therapy Overview

The implanted components of the Inspire therapy system consist of the Inspire 3150 Generator, and the Inspire 4063 Stimulation Lead (Figure 4).

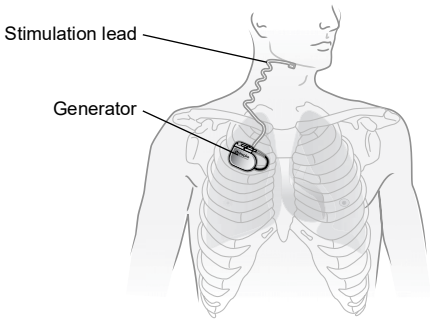


Figure 4. *Inspire system implanted components*

When therapy is on, the Inspire system detects the patient's respiratory effort and maintains airway patency with mild stimulation of the hypoglossal nerve.

Therapy settings are stored in the generator and configured by the physician using an external programmer.

The patient uses their Inspire Sleep Remote to turn therapy on before they go to sleep and to turn therapy off when they wake up. The sleep remote also provides the ability to pause therapy and adjust stimulation amplitude within physician-defined limits.

Indications for Use

Adults
Inspire Upper Airway Stimulation (UAS) is used to treat a subset of patients with moderate to severe obstructive sleep apnea (OSA) (apnea-hypopnea index [AHI] of greater than or equal to 15 and less than or equal to 100).

Inspire UAS is used in adult patients 22 years of age and older who have been confirmed to fail or cannot tolerate positive airway pressure (PAP) treatments (such as continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BPAP] machines) and who do not have a complete concentric collapse at the soft palate level.

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

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

Pediatrics
Inspire UAS is also indicated for OSA patients ages 18 to 21 years with moderate to severe OSA (15≤AHI≤100), and pediatric patients ages 13 to 18 years with Down syndrome and AHI severe OSA (10≤AHI≤50) who:

- Do not have complete concentric collapse at the soft palate level,
- are contraindicated for, or not effectively treated by, adenotonsillectomy,
- have been confirmed to fail, or cannot tolerate, PAP therapy despite attempts to improve compliance, **or**
- have followed standard of care in considering all other alternative/adjunct therapies.

Contraindications

Contraindications for the use of Inspire UAS therapy include the following:

- Central + mixed apneas > 25% of the total apnea-hypopnea index (AHI)
- Any anatomical finding that would compromise the performance of upper airway stimulation, such as the presence of complete concentric collapse of the soft palate
- Any condition or procedure that has compromised neurological control of the upper airway
- Patients unable to or do not have the necessary assistance to operate the sleep remote
- Patients who are pregnant or plan to become pregnant. UAS therapy has not been evaluated for safety or efficacy during pregnancy.
- Patients with an implantable device that may be susceptible to unintended interaction with the Inspire system. Consult the device manufacturer to assess the possibility of interaction.
- Patients who require magnetic resonance imaging (MRI) other than what is specified in the MR Conditional labeling

Warnings

- **Training —** Physicians must be trained in the proper use and surgical procedure before implantation or operation of the device.
- **Pediatrics —** The safety of upper airway stimulation has not been evaluated in clinical studies for patients less than 18 years of age in the general patient population. There may be increased risk of nerve injury and stimulation-related adverse events in this population, particularly in younger children (e.g., less than 12 years of age).
- **Pediatric patients with Down syndrome —** who have not undergone adenotonsillectomy have not been studied as part of the clinical study.
- **Components —** The use of components not provided by Inspire Medical Systems may result in damaged components, improper operation, or increased risks to the patient.
- **Diathermy —** Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with the Inspire system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

  Diathermy can also damage the implanted system components, resulting in loss of therapy and requiring additional surgery for system explantation and replacement. Advise your patient to inform all their healthcare professionals that they should not be exposed to diathermy treatment.

  Injury to the patient or damage to the device can occur during diathermy treatment when:
  - The generator is turned on or off
  - Diathermy is used anywhere on the body—not just at the location of the implanted Inspire system
  - Diathermy delivers heat or no heat
  - Any component of the Inspire system (lead(s) or generator) remains in the body
- **Transcranial Magnetic Stimulation (TCMS/TMS):** Avoid undergoing transcranial magnetic stimulation. Exposure to this treatment has the potential to cause device and/or tissue damage.
- **Magnetic Resonance Imaging (MRI) —** An MRI is a type of medical imaging that uses magnetic fields to create an internal view of the body. If certain criteria are met and the warnings and precautions provided by Inspire are followed, patients with an MR Conditional device are able to undergo an MRI scan. For details, refer to the “MRI Guidelines for Inspire UAS Therapy” manual at manuals.inspiresleep.com.

  Do not bring the sleep remote into the MRI environment. Bringing the remote into the MRI scanner room could cause damage to the remote and make it unable to function.

  The patient is only eligible for certain MRI scans. If the precautions provided by Inspire are not followed, exposure to MRI can damage your generator or lead(s), cause serious injury, or result in unintended stimulation.
- **Sleep remote Use —** When operating their Inspire Sleep Remote, patients should use special care near flammable or explosive atmospheres. The consequences of using the battery-powered sleep remote near flammable or explosive atmospheres are unknown.

- **Body Mass Index (BMI) —** Data on BMI >40 was not studied on a significant number of patients in post-market registries and clinical trials. Safety and effectiveness of Inspire UAS for the BMI>40 patient population is unknown at this time.
  - Pediatric patients with Down syndrome and a BMI index over the 95th percentile on the Centers for Disease Control and Prevention neurotypical growth curves have not been studied.

Precautions

MRI Conditions for Use

The Inspire 3150 Generator and the Inspire 4063 Stimulation Lead are MR Conditional. If certain criteria are met and the warnings and precautions provided by Inspire are followed, patients with an MR Conditional system are able to undergo an MRI scan. For details, refer to the “MRI Guidelines for Inspire UAS Therapy” manual at manuals.inspiresleep.com.

General

- **Expiration date —** Do not use any Inspire system product after its expiration date.
- **Component handling —** Precautions related to component handling during the implant procedure are located on page 17.
- **Storage temperature ranges**
  - Store the generator at ambient room temperatures.
  - Do not expose the stimulation lead to temperatures above 55 °C (131 °F) or below -10 °C (14 °F).
- **Do not reuse —** Contents sterile unless package has been opened or damaged. Any attempt to reprocess the device for subsequent reuse may adversely affect the integrity of the device or lead to deterioration in performance.

Electromagnetic Compatibility and Medical Procedures

For information on MRI, reference “Warnings” on page 9 and the “MRI Guidelines for Inspire UAS Therapy” manual at manuals.inspiresleep.com

For information on diathermy, see “Warnings” on page 9.

The generator is designed to ensure immunity from most common sources of electromagnetic disturbance. In most cases, turning off the electromagnetic disturbance source, or moving away from the electromagnetic disturbance source, will return the generator to normal operation. Extremely strong sources of electromagnetic disturbance could interfere with normal generator operation, causing the generator to reset and requiring the generator to be reconfigured. To reduce the possibility of electromagnetic interference (EMI), patients are recommended to use therapy only while asleep.

Medical Environment

Electrocautery, irradiation, lithotripsy, RF-ablation, x-ray, and fluoroscopy are typical electromagnetic disturbance sources in hospital and clinical environments. Medical treatments that use ultrasonics, defibrillation, or radiation can adversely affect the Inspire system. Ensure that the Inspire generator is turned off prior to these medical treatments.

- **Electrocautery —** Electrocautery tools used near or in contact with the generator or lead(s) can cause tissue damage, uncomfortable stimulation, or damage to the generator. Bipolar electrocautery should be used if alternatives are not available. Unipolar electrocautery can be transmitted along the lead body and could cause nerve damage. If electrocautery must be used in the vicinity of the generator, therapy should be turned off.
- **Radiation therapy —** The generator should not be directly irradiated by therapeutic levels of ionizing radiation (such as produced by cobalt machines or linear accelerators used for cancer treatment) because of the risk of permanent damage to the generator circuitry. If such therapy is required in the vicinity of the generator, shield the device and confirm its function after treatment.
- **Radiofrequency ablation (RFA) —** RFA should not be used directly over the implant sites.
- **X-ray and fluoroscopy —** Exposure to diagnostic x-ray or fluoroscopic radiation should not affect the generator or the lead(s).
- **Therapeutic ultrasound —** Exposure to high ultrasonic frequencies may result in damage to the generator or lead(s). It is not recommended to use high-output ultrasonic devices, such as an electrohydraulic lithotriptor or bone growth stimulator on patients with an implanted generator.
- **Ultrasonic scanning —** While there is no danger to the patient, ultrasonic scanning equipment could cause mechanical damage to the generator or the lead(s) if used directly over the implant sites.
- **Defibrillation/cardioversion —**
  - Utilize biphasic waveforms and minimize the energy delivered.
  - Position paddles as far as possible from implanted Inspire components.
  - Consider an anteroposterior paddle placement for both left and right sided implants. For this configuration, place the anterior pad over the apex of the heart, under the left breast. Place the posterior pad under the left scapula in line with the anterior pad
  - Following defibrillation, confirm normal system operations.

Home or Work Environment

Based on laboratory tests of the generator, the device should not be affected by the normal operation of electrical equipment, household appliances, electric machine shop tools, microwave ovens, internal combustion engines, low-powered radio, or microwave frequency transmitters. All such equipment should be kept in good repair and properly grounded to avoid the possibility of electrical shock or interference with the proper operation of the generator.

Inspire therapy is intended for use during sleep only and should be turned off otherwise.

- **Equipment operation —** Patients should not operate potentially dangerous equipment, such as power tools, while therapy is on.
- **Theft detectors —** Theft detectors have been known to cause inadvertent and potentially uncomfortable stimulation in implanted stimulation systems. Patients should use care to avoid prolonged exposure to theft detectors and be aware in the presence of such systems.
- **High-powered electric fields —** Consult Inspire Medical Systems when the patient will be in an area where contact with current carrying conductors is possible or near high-powered electromagnetic fields radiated by arc welding units, induction furnaces, induction stoves, resistance welders, radio or microwave frequency transmitters, etc.
- **Mobile and cellular phones —** Maintain a separation of at least 15 cm (6 in) between a phone and the generator.

Pediatric Use

For pediatric patients aged 13-21, OSA may possibly resolve without intervention. Therefore, a decision to surgically implant a device in this population should be discussed with the treating sleep physician. Even though the device may be explanted, when absolutely necessary, at times the cuff around the hypoglossal nerve may be left implanted permanently. While there is no definite way to identify who will remit in this population, please consider factors which may influence persistence OSA (e.g. comorbidities, ethnicity, obesity, and male gender.) Please consider following alternative/adjunct therapies prior to Inspire UAS therapy:

- Adenotonsillectomy in appropriate patients (however, some patients are contraindicated for adenotonsillectomy)
- Intensive behavioral therapy and/or desensitization therapy to improve PAP adherence
- Medical pharmaceutical interventions
- Other less invasive interventions, e.g. lifestyle changes, positional therapy, oral appliances, and nasal devices

In younger patients undergoing this surgical implantation, please consider the need for a lifetime of serial surgical reimplantation for battery replacements, which may potentially be associated with future surgical complications.

Pediatric Down syndrome use

For pediatric patients with Down syndrome, the patient's physician or a specialist in Down syndrome care should consider unique factors such as growth profile and cognitive capabilities for using the Inspire UAS system, prior to implant.

Adverse Effects

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

- Damage to blood vessels in the vicinity of implant
- Excessive bleeding
- Nerve trauma or damage
- Allergic and/or rejection response to the implanted materials
- Infection
- Local irritation, seroma, hematoma, erosion, or swelling
- Persistent pain, numbness, or inflammation at the implant site
- Discomfort from the stimulation
- Tongue movement restrictions, irritation resulting from tongue abrasions on preexisting sharp or broken teeth
- Tongue soreness or weakness
- Problems with swallowing or speaking
- Tongue paresis and atrophy
- Undesirable change in stimulation over time, possibly related to tissue changes around the electrode(s), shifts in electrode position, loose electrical connections, or lead fractures
- Fibrosis to the extent that it makes it difficult to remove the system without damaging surrounding structures
- Dry mouth
- Other acute symptoms (i.e., headaches, coughing, choking, dysphasia, and speech-related events)
- Insomnia
- Pneumothorax
- Rhabdomyolysis

Storage and Handling

Recommendations for storage and handling of the generator and the lead are provided in this section. Inspire Medical Systems sterilizes the generator and the lead with ethylene oxide (EtO) prior to shipment. The generator cannot be resterilized or reused.

Information about precautions for handling components is located on page 17.

Generator

Inspect the generator sterile package prior to opening. If the generator package is damaged, the generator may be damaged as well. Return the damaged package along with the product to Inspire Medical Systems; see the back cover of this manual for addresses.

The generator box includes a sterilization indicator. This indicator is green after the device has been sterilized. **Do not use the generator if the indicator is red, dark red or black.**

Handling and Storage: Acceptable	Handling and Storage: Unacceptable
Transport generator within the following environmental temperature limits: -35 °C (-31 °F) to +58 °C (+136 °F). A full or partial electrical reset condition may occur at temperatures below -18 °C (0 °F). Store the generator at ambient room temperatures.	Do not implant the generator if it has been dropped on a hard surface from a height of 30 cm (12 in) or greater.

Resterilization
The generator cannot be resterilized or reused. • Generators cannot be resterilized. If the sterile package seal is broken, or if the packages are otherwise damaged, do not use. • Return the package and product to your local Inspire Medical Systems representative, or see the back cover for mailing address.

Stimulation Lead

If the lead sterile package seal is broken or the package is otherwise damaged, return the package to Inspire Medical Systems. The lead cannot be resterilized or reused.

Handling and Storage: Acceptable	Handling and Storage: Unacceptable
Store and transport the stimulation lead within the following environmental temperature limits: -10 °C (14 °F) to +55 °C (+131 °F). Only use sterile-gloved hands to handle the lead; rinse sterile surgical gloves in sterile water before handling the lead. Protect the lead from materials that shed lint and dust. Exercise care and appropriate instrument selection when handling the stimulation lead cuff with a surgical instrument.	Do not implant a lead that was dropped. Avoid excessive traction or sharp instruments. Avoid severe bending, kinking, stretching, or handling with surgical instruments. Do not immerse the lead in mineral oil or silicone oil.

Resterilization
The lead cannot be resterilized or reused. • If the sterile package seal is broken, or if the packages are otherwise damaged, do not use. • Return the package and product to your local Inspire Medical Systems representative, or see the back cover for mailing address.

Physician Training

Prior to implanting an Inspire system, surgeons will complete a training class defined by the manufacturer. Sleep physicians and sleep technicians will complete a training class defined by the manufacturer.

System Implant

This section describes a general implant procedure for the Inspire system.

Implantable Components

The Inspire system includes the following implantable components (Figure 5):

- Inspire 3150 Generator (with lead connector port)
- Inspire 4063 Stimulation Lead

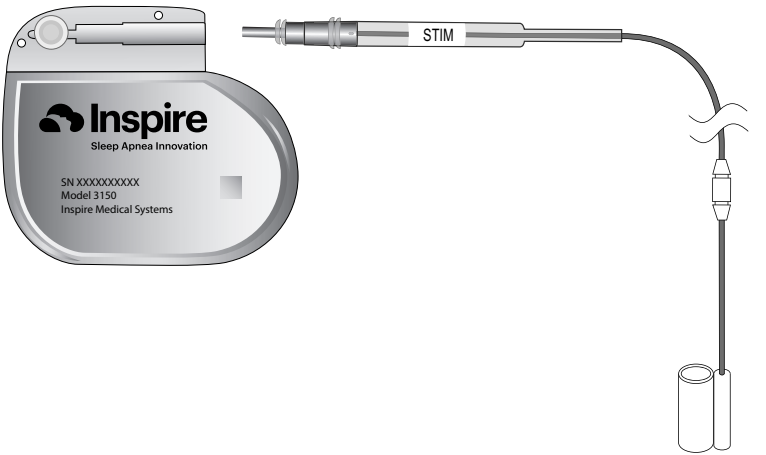


Figure 5. *Generator and Stimulation Lead*

Procedure Overview

The implant procedure begins with preoperative planning. It is recommended that the stimulation lead be the first Inspire component to be implanted. Secondly, a subcutaneous pocket is created for the generator. The connector end of the stimulation lead will be tunneled to this pocket. Once the lead connector end is within the generator pocket, the lead is connected to the generator and the generator is secured in the subcutaneous pocket.

Patient Preparation

- Ensure the tongue is visible during the surgical procedure in order to observe the response to intraoperative test stimulation.
- The recommended body side for system implantation is the right side.
- If other active implanted devices are present, plan incision and tunneling locations to keep the Inspire system at least 15 cm (6 inches) away from the other devices.
- The patient's head and neck should be positioned to provide optimal access to the hypoglossal nerve.
- Iodine-impregnated adhesive drape over entire surgical area is recommended.
- Use only short-acting paralytic agent to preserve tongue response.
- A nerve monitoring system is recommended to locate the hypoglossal nerve and confirm nerve recruitment.
- The patient should be given antibiotics preoperatively and may be given antibiotics postoperatively, at the surgeon's discretion.

Surgical Materials

An Inspire system implant requires typical surgical equipment used during neck surgeries. The following is a list of additional materials typically used during the system implant procedure:

- Sterile sleeve, bag or equivalent (to bring the telemetry cable into the sterile field)
- Finer right angled forceps or hemostat (for stimulation lead cuff electrode placement)
- A nerve monitoring and stimulation system (to locate the hypoglossal nerve and confirm nerve recruitment)

Precautions for Handling Components

- The implanted components of this system should be carefully handled to avoid damage by excessive traction or sharp instruments. Any component showing signs of damage should not be used.
- Generator drop — If the generator is dropped more than 30 cm (12 in) onto a hard surface, it should not be used.
- Setscrew cautions — Counterclockwise rotation of a set screw beyond one or two revolutions while retracting it from the connector port may disengage the set screw from the connector block. A hex wrench is provided with the generator packaging. If using a different tool, review both its instructions for use, as well as the following information to ensure it is appropriate for this implant procedure.
- Set Screw Seal — Use care when inserting the hex wrench to avoid damage to the seals. Insert the hex wrench perpendicular to the seal.
- The lead should be handled with great care at all times. Any severe bending, kinking, stretching, or handling with surgical instruments may cause permanent damage to the lead body or the cuff. Do not implant a lead that has been dropped.
- The lead attracts small particles, such as lint and dust; to minimize contamination, protect the lead from materials shedding these substances. Handle the lead with sterile surgical gloves that have been rinsed in sterile water.
- Do not immerse the lead in mineral oil or silicone oil.

Stimulation Lead Implant

The stimulation lead is designed with a cuff that is placed around the hypoglossal nerve after the nerve is exposed.

The following is an overview of the recommended process for implanting the stimulation lead:

- Expose the hypoglossal nerve.
- Place the stimulation lead cuff around the nerve and irrigate the cuff and nerve with sterile saline.
- Secure the stimulation lead anchor with permanent sutures.

Exposing the hypoglossal nerve

1. Make a incision between the hyoid and mandible.
2. Retract the necessary anatomic structures to expose the distal hypoglossal nerve.
3. Once the nerve is identified, it may be stimulated at a low setting (typically 0.2–0.5 mA) using an external nerve stimulator to confirm nerve function. Do not over stimulate the nerve with the external device.

⚠ **Cautions:**

- Avoid excess tension to the nerve and supporting tissue while exposing the nerve and placing the cuff.
- Preserve the small nutrient blood vessels along the nerve fibers.
- Maintain hemostasis. Fluid residuals increase the chances of hematoma formation and infection.

Placing the stimulation lead cuff

To place the stimulation lead cuff, the cuff's short inner and long outer flaps (Figure 6) are wrapped around the hypoglossal nerve.

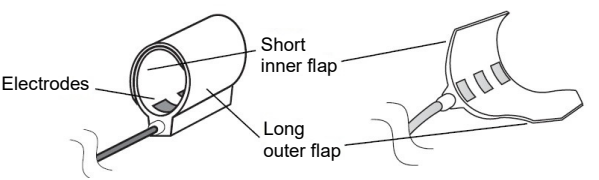


Figure 6. *Stimulation lead cuff flaps*

Steps 1-5 illustrate one method to place the stimulation cuff. Refer to Figure 7.

1. Using a right-angled forceps (or equivalent) positioned under the nerve, grasp the long outer flap.

⚠ **Caution:** Do not force the cuff into position. Be sure that a sufficient opening has been cleared. Forcing the cuff into position may result in nerve damage.

2. Carefully bring the outer flap underneath and around the nerve and then unfurl so it lies flat.
3. Ensure the short flap covers the nerve, then release the outer flap to close around the inner flap.

Cautions:
- Be sure that the cuff flaps are properly placed.
- Do not suture the cuff around the nerve. The cuff is designed to expand and contract with the nerve. Suturing the cuff in place may result in nerve damage.

4. Ensure all target nerve branches are enclosed within both flaps, and without undue tension or filmy adhesions interfering with flap closure and settling.
5. Irrigate between the nerve and cuff (e.g. use 18–20 gauge Angiocloth) with sterile saline to facilitate adequate electrical contact between the electrodes and the nerve.

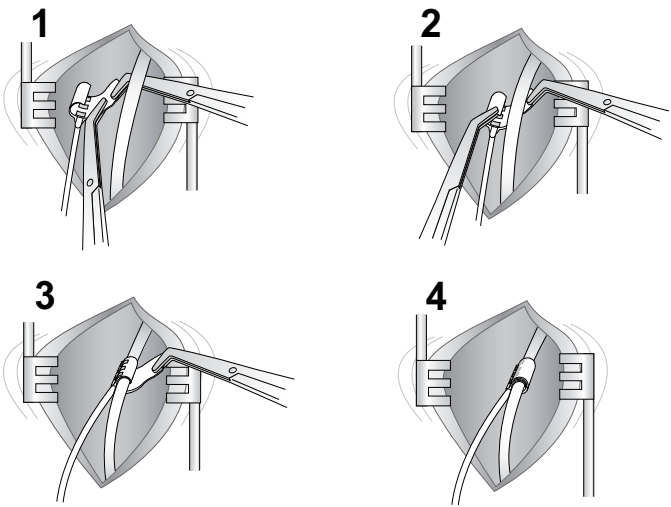


Figure 7. *Placing the cuff around the hypoglossal nerve*

Securing the Stimulation Lead (Figure 8)

1. Maintain the cuff and stimulation lead body parallel to the nerve to avoid placing torque or tension on the nerve.
2. Secure the stimulation lead with adequate strain relief by creating a lead loop in between the stimulation lead cuff and the anchoring site (e.g. digastric tendon or muscle).
3. Using both anchor recesses, tie permanent sutures to the anchor, then secure the anchor to the digastric tendon or muscle using the sutures.
4. It is recommended that the physician not close the neck incision until all system components are implanted and tested. Consider gently packing the neck incision with 4x4 gauze soaked in a saline/antibiotic solution. Remove such packing with care prior to closing the incision so as not to dislodge or disrupt the cuff placement.

⚠ **Cautions:**

- Place sutures only around the lead anchor and not the lead body.
- Surgical instruments should not be used to handle the lead body directly. The lead and lead insulation are easily damaged. Care should be used when handling the lead. Surgical instruments may be used for handling the lead anchor.

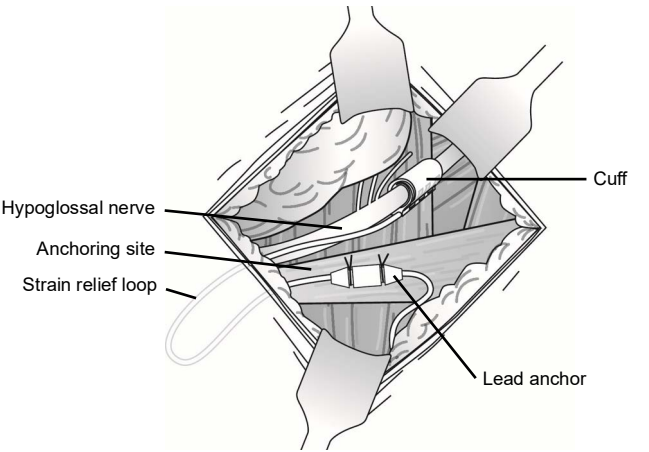


Figure 8. *Anchoring the stimulation lead*

Forming the Generator Pocket

When selecting the location for the generator pocket, consider patient lifestyle factors, such as the use of firearms, carrying backpacks, and other work or recreation-related activities. The following instructions reflect the typical generator pocket location.

1. Make a 4–5 cm (1.6–2.0 in) incision over the second rib space.
2. Make a subcutaneous pocket of sufficient size to contain the generator and any excess lead wrap, which can typically be expected.The typical pocket should be created no deeper than 2.5 cm (1.0 in) below the skin to allow for reliable communication between the generator and external devices.
3. Place two anchoring sutures, permanent braided 2.0 silk or equivalent, in the pectoralis major fascia 2–3 cm apart.

Tunneling the Lead

Use an appropriate surgical tool to pass the lead connector from the point of lead implantation to the subcutaneous pocket, avoiding sharp angle bends of the lead body.

1. Perform blunt dissection under direct visualization from both incisions along the desired tunneling path.
2. A sterile tunneling tool (Figure 9) is provided with the stimulation lead packaging. If using a different tool, review both its instructions for use, as well as the following information to ensure it is appropriate for this implant procedure.
   - Prior to assembly, the rod may be bent to aide tunneling. Generally, it is better to make multiple gentle bends than a single sharp bend.
   - The tool is assembled by threading the tip and the collet assembly to the stainless steel rod. Attach the tip first and the collet only after the tunnel is established.

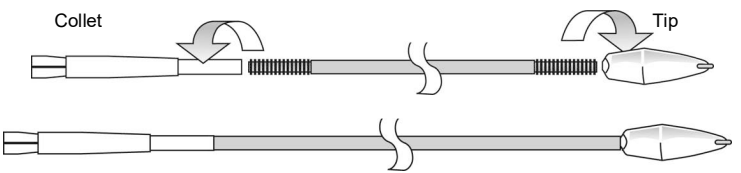


Figure 9. *Figure 9. Tunneling tool components*

3. Subcutaneously advance the tunneling tool between the lead incision and the generator incision until the tip is exposed. Complete the tunnel before attaching the collet.

Cautions:

- Deep tunneling is not desirable. Pass the lead superficially to avoid damage to deep structures.
- It is recommended to maintain a sub-platysmal plane while tunneling.
- To avoid damage to the lead or body tissue, do not use excessive force or surgical instruments when using the tunneling tool.
- Tunneling the lead under the clavicle bone is not recommended. A lead tunneled under the clavicle bone creates an increased risk of damage to veins and/or arteries.
- To avoid damage to the collet, do not attach it to the tunneling tool until the tunnel is established from the lead implant site to the generator pocket.
- To accommodate future growth for pediatric patients:
  a. Extra lengths of lead strain relief should be formed at both ends of all tunnels.
  b. Avoid breast tissue in female patients during implant.

4. Insert the lead connector into the tunneling tool collet as follows:
a. Slide the collet sleeve down toward the tunneling tool tip to allow the lead connector to be inserted into the collet.
b. Insert the pin of the lead connector into the collet of the tunneling tool (Figure 10 A)
c. Slide the sleeve over the collet to lock the connector pin in place (Figure 10 B).
d. It is not necessary to exert excessive force to secure the sleeve over the collet.

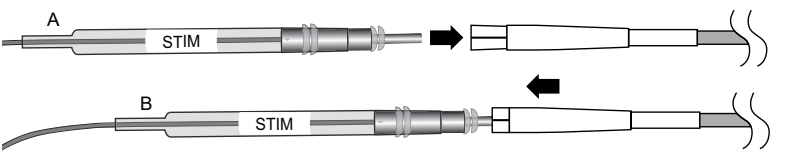


Figure 10. *Inserting lead connector into tunneling tool collet*

5. Gently pull the lead out through the exit site in the generator pocket.

Caution:
Be sure the lead is routed so as to avoid sharp bends or kinks in the lead body.

6. Remove the lead from the tunneling tool by sliding back the sleeve from the collet.

Caution:
Leave a small amount of excess lead length at both sides of the subcutaneous tunnel so that normal body motions do not stretch the leads' body. The patient may be able to feel this stretching and it may cause damage to the lead.

Connecting the Lead and Generator

⚠ **Caution:** Saline or bodily fluids in the generator connector port may reduce battery longevity.

- Do not allow saline or bodily fluids to enter the generator connector port.
- Confirm that lead connector is dry prior to inserting it into the generator port.
- Use care when inserting the hex wrench to avoid damaging the seals, inserting the hex wrench in the center of the seal while holding it perpendicular (90 degree angle) to the surface of the generator.
- Confirm that setscrew seal is fully closed after securing the lead in place.

Connect the stimulation lead to the generator

1. Wipe off any body fluids from the stimulation lead connector.
2. Grasp the strain relief (Figure 11 A) segment of the lead (approximately 3 cm [1.2 in] from the connector end) and insert the lead connector pin (Figure 11 B) into the generator connector port (Figure 11 C).
   - Make sure the lead connector is fully inserted into the generator connector port by verifying that the lead connector pin is visible past the set screw block (Figure 11 D).
   - If the lead tip is hard to visualize, verify the large seals (Figure 11 E) on the lead are past the insertion indicator (Figure 11 F).

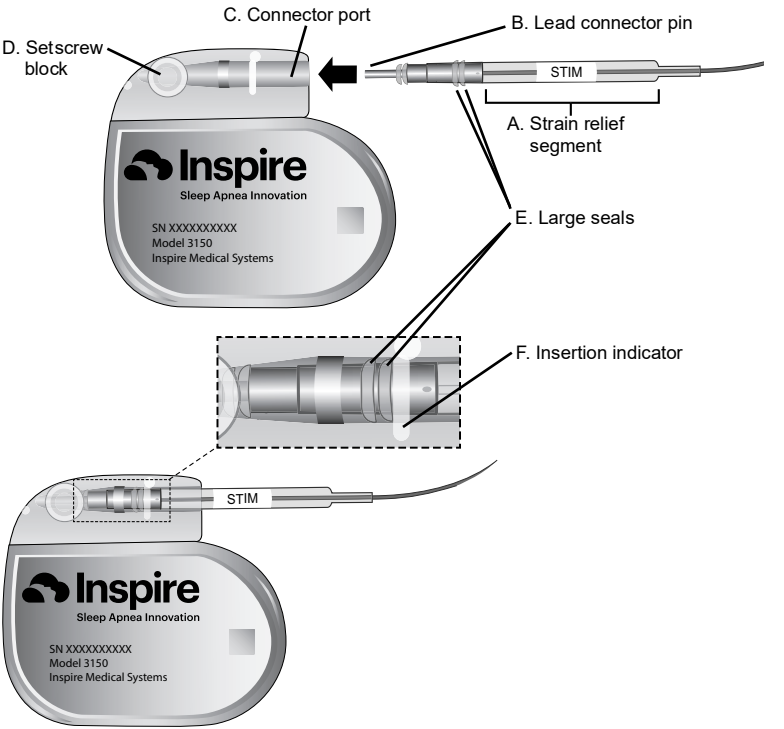


Figure 11. *Insert stimulation lead connector into generator connector port*

3. Use the hex wrench to tighten the set screw on the port (Figure 12). Insert the wrench at a 90 degree angle from the surface of the generator and directly in the center of the seal. Tighten until resistance is felt, and then continue until audible clicking is heard from the wrench. After the set screw is tightened, pull firmly on the lead strain relief segment immediately adjacent to the generator—NOT the lead body—to confirm that the set screw has secured the lead in place.Verify the lead tip is visible past the set screw block. After removing the wrench, confirm the seal covering the setscrew is fully closed and undamaged.

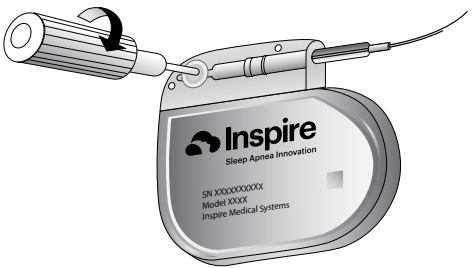


Figure 12. *Tighten the setscrew*

Implanting the Generator

Excess lead length is desirable at the distal lead location and within the generator pocket to ensure body motions do not stretch the lead or cause discomfort. If necessary, gently wrap excess lead body behind (i.e. deep to) the generator (Figure 13) and position the generator and wrapped excess lead body in the pocket. Ensure that the generator logo is facing up (i.e. superficially) toward the skin.

Figure 13. *Wrap excess lead length*

⚠ **Caution:** When placing the generator and lead into the subcutaneous pocket:

- Do **not** grip the lead or generator with surgical instruments.
- Do **not** place the lead under tension. Ensure there is a substantial amount of excess lead length in the generator pocket and at the stimulation lead distal site to prevent body motions from stretching the lead.

System Test

Perform intraoperative testing prior to closing to confirm proper lead placement and lead-generator connection. Optionally, interim system testing can be performed earlier in the procedure at the physician's discretion.

1. Start a programming session utilizing the Inspire 2740S Programmer and the Inspire 2740C Programmer Cable with the generator by selecting **Connect to Generator** from the programmer Start screen.
2. Test the stimulation function as follows:
   - Place the programmer cable into a sterile sleeve and hold the telemetry head centered over the generator.
   - Test stimulation levels using the Inspire programmer (see the programming manual for instructions). Conduct intraoperative test stimulation while observing patient muscle response to stimulation. Apply saline to the cuff to facilitate electrical contact of the cuff electrodes with the nerve.
   - Verify that bipolar stimulation gives the appropriate response. Reposition the stimulation lead cuff if necessary.
   - Record the lowest functional level using the Inspire programmer.
   - Once sensor function has been verified, turn the therapy off.
3. Following the system functional check, verify that the therapy is off and the stimulation amplitude is programmed to 0 volts. It is recommended to keep the therapy off for approximately one month after the implant surgery to allow for healing and encapsulation of the stimulation lead.
4. If it is necessary to disconnect the lead from the generator, use care to insert the hex wrench through the set screw seal. Carefully disconnect the stimulation lead connector from the generator.

> ⚠ **Caution:** Use care to not loosen the generator set screw more than necessary, which can result in the set screw unseating from the connector and damaging the generator set screw.

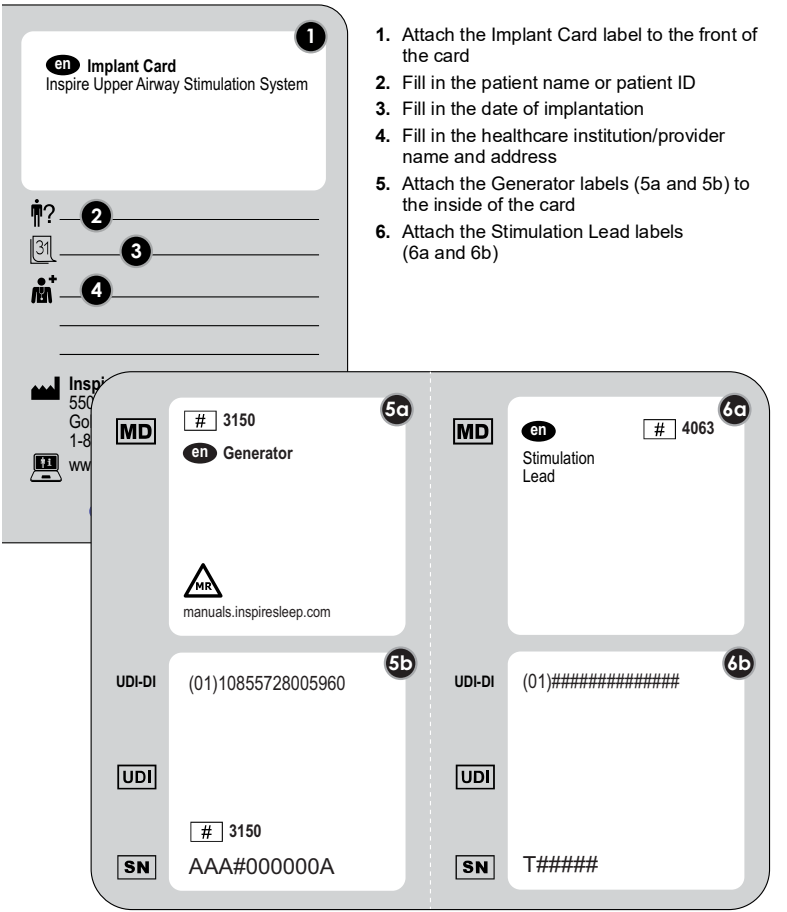
Completing the Implant Procedure

After testing, complete the implant procedure:

1. Secure permanent sutures through both generator suture holes.
2. Irrigate all incision sites before closing.
3. Close the surgical incisions.
4. At the physician's discretion, antibiotics may also be administered postoperatively.
5. Take at least one anterior-posterior and one lateral x-ray to document the location of all system components. Both head/neck and chest x-rays may be needed to fully capture the implanted system.
6. Place pressure dressings on the incision sites.

Patient Implant Card

Patients should carry their implant card with them at all times. The clinician should use the card and labels supplied and place them on the card as follows.



1. Attach the Implant Card label to the front of the card
2. Fill in the patient name or patient ID
3. Fill in the date of implantation
4. Fill in the healthcare institution/provider name and address
5. Attach the Generator labels (5a and 5b) to the inside of the card
6. Attach the Stimulation Lead labels (6a and 6b)

Physician Instructions to Patient

Give the patient information concerning the Inspire system. This should include the 3150 Patient Manual and the Patient Implant Card.

Patients should be instructed as follows:

- It is normal to feel some discomfort from the incisions and to have some pain at the implant sites for 2–6 weeks.
- It is best to avoid bending, twisting, and large arm movements for several weeks after the implant procedure, as such movements could impair the healing process. This time period allows the lead and generator to fix themselves more securely in place.
- Avoid physical activities that could damage the implant site or implanted device.
- Inform personal physicians, consulting physicians, or dentists that they have an implanted stimulation system.
- Carry their Inspire Implant Card at all times.

The “Precautions” section on page 10, which includes information about cellular phones and electromagnetic interference in the home or work environment, should also be conveyed to the patient.

Postoperative Follow-up

Follow up with normal postoperative care. A 7–14 day check of surgical incision healing is recommended.

Regular patient follow-up should be scheduled to monitor system status and therapy effectiveness.

Patient Registration

The implanted components of the Inspire system (generator and lead) are subject to the Food and Drug Administration’s Medical Device Tracking Requirements (21 CFR 821). A device registration form must be completed. Typically, the Inspire representative will fill out an online form, however the clinician can complete the form that is included with the system and return the printed form to Inspire Medical Systems. The information provided on this form is required for Inspire to meet government obligations for device tracking, product safety, effectiveness, performance and government event reporting and is a public health disclosure under Section 164.512(b)(1)(iii).

Therapy Activation

Inspire therapy should be activated approximately 4 weeks after the implant procedure to allow for healing. At the activation appointment, the patient should be given the Inspire Sleep Remote and corresponding manual.

Therapy Titration

At least one sleep study will be needed approximately 4–8 weeks after therapy activation to titrate stimulation settings. Additional titration sleep studies may be needed to improve therapy effectiveness and patient comfort.

Surgical Revision and Explant

Lead Repositioning

- If a lead becomes displaced, any repositioning should be attempted as soon as possible, before scar tissue builds up.
- If the lead must be repositioned (or removed) proceed with caution to avoid damage to surrounding tissue.
- Extreme forces used during removal can damage the lead(s) or result in dismantling of the lead(s).
- If removal is unavoidable, return the removed lead, or portion thereof, to Inspire Medical Systems.
- After any revision of the stimulation lead, follow the healing period for an initial implant.

Generator Replacement

- Use x-ray imaging to plan the surgical approach to avoid the implanted lead(s).
- Make an incision to expose the generator. During dissection, take care not to cut the lead body or bodies or damage any lead body insulation.
  - **CAUTION:** Avoid the use of unipolar electrocautery. Unipolar electrocautery can be transmitted along the lead body leading to permanent nerve damage or damage to the generator.
  - Prior to removing the outgoing generator, carefully cut any anchoring sutures, then carefully remove the generator enough to access the set screws. Use care during generator removal and avoid forces that may damage the lead(s).
- Loosen the set screw(s) using the wrench provided with the new generator. Use gentle traction to remove the lead(s) from the expired generator.
  - **CAUTION:** To avoid damaging the lead, grasp lead(s) by the strain relief segment and not the lead body during removal from the generator.
- If a sensor lead has been previously implanted, the lead can be abandoned or explanted. See “System or Generator Explant” on page 31.
- Ensure the lead is wiped clean and dry prior to inserting into the new generator.
- Connect the stimulation lead to the generator.
- Use both anchoring holes to secure the new generator.
- Before final closing, carefully examine the generator pocket to eliminate any micro-bleeding and make sure hemostasis is established.

- Return the expired generator to Inspire Medical Systems in a biohazard container and mailer for analysis and disposal. Your local Inspire support personnel can facilitate this process as needed.
- After revision of the generator, the system may be activated immediately, at the surgeon's discretion.

System or Generator Explant

- Extreme forces used during removal can damage the lead(s).
- A lead that has been cut off should have the remaining lead end sealed.
- Lead removal may not be possible due to the risk of damaging surrounding structures. The decision to remove the lead(s) or leave them in place is made between the physician and the patient on a case-by-case basis. The implications of both options should be discussed, for example:
  - Removing the lead(s) may extend the duration of the surgical procedure, possibly requiring additional incision(s), and the dissection of fibrotic tissue that may have formed.
  - A partially explanted system may be MR unsafe, which will prevent the patient from receiving an MRI. Furthermore, patients must be made aware that they need to notify medical personnel that they still have implanted lead(s) even if the generator has been removed. A fully intact, abandoned sensor lead does not prevent a patient from receiving an MRI. See "MRI Conditions for Use" on page 10.
- Return all explanted components to Inspire Medical Systems for disposal.

Explant Disposition

When replacing or explanting a generator or lead, return the generator or lead to Inspire Medical Systems for analysis and disposal. See the back cover of this manual for mailing address.

Clinical Summary

Stimulation Therapy for Apnea Reduction (STAR) Clinical Trial

The Inspire Upper Airway Stimulation (UAS) system was evaluated in a multi-center trial at study centers in the United States and Europe for the indication of moderate to severe obstructive sleep apnea (OSA) in patients who were not effectively treated by continuous positive airway pressure (CPAP).

Patients Studied

The study enrolled 929 OSA patients. These patients were evaluated against patient selection criteria that included moderate to severe OSA, a BMI (body mass index) less than or equal to 32, and the absence of a complete concentric collapse at the level of the soft palate. Following the evaluation period, 126 patients met all selection criteria and proceeded to implant. All 126 implant procedures were successful, and 124 of the 126 implanted patients provided evaluable data through at least 12 months. The STAR trial was an intent-to-treat study. Therefore, the 2 patients who did not provide evaluable data through 12 and 18 months post-implant are assumed to be non-responders and were included in the evaluation as such. The patient demographics for the STAR trial are included in Table 1. The patients' baseline AHI showed a mean of 32.0 and a median of 29.3, and the baseline ODI showed a mean of 28.9 and a median of 25.4.

Table 1. STAR Trial Subject Demographics

Continuous Measures	**Mean** **N = 126**	**Median**
Age, year	54.5	55
Body Mass Index, kg/m2	28.4	29.2
Neck Size, cm	41.2	41.9
Systolic BP, mmHg	128.7	128
Diastolic BP, mmHg	81.5	80.5
Male	105 (83%)	Total N = 126
Race Caucasian African American Hispanic Asian Others*	 122 (97%) 0 (0%) 1 (1%) 1 (1%) 2 (2%)	 * 1-Surinam, 1-Turkey

Study Design and Methods

The STAR trial was a multi-center, prospective trial with a 12-month single arm study and a randomized controlled therapy withdrawal study at 13 months. Following implant of the Inspire system, patients were followed at 1, 2, 3, 6, 9, 12, 13, 15, 18 months, and every 6 months thereafter. The patients' baseline AHI and ODI (oxygen desaturation index) values were the mean results from their screening (pre-implant) and 1-month (post-implant but prior to therapy activation) sleep studies. Baseline results were compared to the 12-month results to determine the percentage of patients who experienced a clinically meaningful reduction in the severity of their OSA in terms of their AHI and ODI scores. For this study, a clinically meaningful reduction in AHI and ODI was defined as (1) a 50% reduction in the AHI compared to the pre-implant screening and 1-month visit (post-implant but prior to therapy activation) and an AHI < 20 events per hour, and (2) a 25% or greater reduction in ODI at the 12-month visit compared to baseline.

Upon completion of the overnight sleep study at the 12-month visit, a randomized controlled therapy withdrawal study was conducted. The first 46 responders were randomized 1:1 to either the therapy maintenance (ON) group or the therapy withdrawal (OFF) group, resulting in 23 subjects in each group. Patients randomized to the therapy withdrawal group had Inspire therapy turned OFF for at least five days. Patients randomized to the therapy maintenance group continued their use of the Inspire system. All randomized patients participated in a sleep study at the 13-month visit. The therapy withdrawal group had the sleep study performed with Inspire therapy OFF, and the therapy maintenance group had the sleep study performed with the Inspire therapy ON. The mean change of AHI for each arm was compared to determine the extent of treatment effect from Inspire therapy.

The percentage of sleep time a patient had an oxygen saturation (SaO_2) level below 90% was recorded during the sleep studies, and two validated quality of life questionnaires were administered at follow-ups through 18 months. The quality of life questionnaire was the Epworth Sleepiness Scale (ESS), which rates a patient's daytime sleepiness, and the Functional Outcomes of Sleep Questionnaire (FOSQ), which assesses the effect of a patient's daytime sleepiness on activities of ordinary living. The hypotheses for the secondary efficacy endpoints, which included the randomized withdrawal study, FOSQ, ESS, and SaO2, were tested according to a hierarchical strategy in order to preserve an overall Type I error rate of 5%.

Study Results

Titration

All subjects underwent polysomnography (PSG) for titration of therapy settings at 2 and 6 months. Additional titration PSG studies were performed as needed. Through 18 months, patients had an average of 3.3 (range 2–6) titration studies.

Safety

Of the 126 patients implanted with the Inspire UAS system in the STAR trial, 124 were followed through 18 months. There were no unanticipated events and only 2 events required surgical intervention. Both events consisted of an generator migrating out of position and were resolved with a surgical procedure performed under local anesthesia to reposition the generator.

Many of the procedure-related adverse events reported are expected with a surgical procedure. The procedure-related events are described in Table 2.

Table 2. Procedure-Related Adverse Events (and the probability of experiencing them in the first 18 months)

Event	Number of Subjects with Event	Percent of Subjects (n=126)
Incision pain	35	28%
Post-operative discomfort	31	25%
Temporary tongue weakness	23	18%
Sore throat from intubation during implant	15	12%
Other post-operative symptoms (such as gastrointestinal (nausea, vomiting, abdominal pain, constipation), body pain (back, knee, wrist, hand), allergy to antibiotics, anxiety, ineffective airway clearance, loss of some taste, inability to void)	14	11%
Headache	8	6%
Mild infection	1	1%

The device-related adverse events are described in Table 3.

Table 3. Device-Related Adverse Events (and the probability of experiencing them in the first 18 months)

Event	Number of Subjects with Event	Percent of Subjects (n=126)
Discomfort due to electrical stimulation	59	47%
Tongue abrasion	30	24%
Other acute symptoms (i.e., headaches, coughing, choking, dysphasia, and speech-related events)	23	17%
Mouth dryness	14	11%
Complaints related to temporary usability or functionality issues with an implanted device	13	11%
Complaints related to temporary usability or functionality issues with an external device	13	10%
Mechanical pain associated with presence of device	10	8%
Mild infection	1	1%

At the completion of the 18-month follow-up visits of all study patients, 75% of device-related events were fully resolved, primarily with either medication, device reprogramming, dental work to fix a jagged tooth, or with the aid of a lower tooth guard used during sleep to prevent tongue abrasions, or no intervention. Twenty-five percent (25%) of device-related events were unresolved at 18 months. Currently unresolved events include reports of discomfort due to stimulation, tongue abrasion and various stimulation related events including dry mouth, headaches, intermittent waking, isolated stimulation sensation events, audible buzzing, and intermittent fatigue. Despite these reported events, patients continued to report high (85%) compliance with the therapy at 18 months.

Two subjects had their devices removed, which required a surgical procedure. One chose to have the generator removed, and the leads were capped and left in the patient. The other had the entire system removed as a precaution due to proximity to an unrelated infection. Both explants were successfully completed without damage to the surrounding structures. There were 3 deaths over the course of the study, all were unrelated to Inspire therapy. There were 32 serious adverse events (SAE), 2 of which were related to Inspire therapy, both involving repositioning of the generator.

Of the 42 patients implanted with the Inspire UAS system in the Pediatric Down syndrome Clinical Study, all patients underwent implant without intraoperative complications, and no patients subsequently had the device removed.

Table 4. Complications after Upper Airway Stimulation in Adolescent Patients with Down Syndrome and Obstructive Sleep Apnea

Event	Number of Subjects with Event	Percent of Subjects (n=42)
Nonserious adverse events		
Tongue or oral pain or discomfort	5	11.9%
Rash at surgical site	4	9.5%
Acute insomnia	2	4.8%
Cellulitis at surgical site	2	4.8%
Cheek swelling	1	2.4%
Perioperative urinary retention	1	2.4%
Oral ulcers	1	2.4%
Post-obstructive central hypoventiliation	1	2.4%
Serious adverse events		
Readmission	5	11.9%[a]
Reoperation	2	4.8%
Pressure ulcer	1	2.4%

[a]Four related to surgery and one unrelated to surgery

The most common post-implant complication was tongue or oral discomfort or pain, which occurred in 5 patients (11.9%) and was temporary. One patient had worsening of central apnea based on the 1-month activation polysomnogram, suggestive of post obstructive central hypoventilation. Four patients (9.5%) had device- or surgery-related readmissions. The readmissions were the result of device extrusion due to the patient picking at the submental incision (resolved after replacement of the extruded device), surgical site infection at the chest incision exacerbated by patient picking (resolved with antibiotics), poorly controlled postoperative pain, and discomfort from sensing the stimulation in the jaw and chest (resolved without intervention). One readmission was not related to either the device or surgery. One additional serious adverse event occurred when a patient had a pressure ulcer from extended positioning during the surgery (resolved without intervention). The reoperation rate was 4.8% (n=2), representing one patient with extruded device and one patient who required revision due to incomplete insertion of the sensing lead. There were no adverse events that led to permanent injury, life-threatening illness, or death.

Efficacy

The sleep studies, which were scored by an independent sleep scoring core lab, showed statistically significant and clinically relevant reductions in the patients' AHI and ODI scores. Table 5 reports the percentage of patients who experienced a clinically meaningful reduction in their OSA severity (i.e., responders). As this is an intent-to-treat study, these results are based on a total of 126 patients even though only 124 patients provided evaluable data through 12 and 18 months. The other 2 patients are assumed to be non-responders and are included in the evaluation as such.

Table 5. Therapy Responders at 12 Months Post-Implant

Responder	Responder Rate at 12-Month Follow-Up	Responder Rate at 18-Month Follow-Up
50% Reduction in AHI from baseline and AHI < 20	66% (83/126)	65% (80/124)
25% Reduction in ODI from baseline	75% (94/126)	80% (99/124)

The average reduction of AHI from baseline to 12 months was 68% and 70% for ODI. Baseline AHI showed a mean of 32.0. In comparison, the AHI at the 12-month PSG study showed a mean of 15.3. Baseline ODI showed a mean of 28.9. In comparison, ODI at the 12-month PSG study showed a mean of 13.9. The patients also had statistically significant improvements in terms of time with SaO_2 < 90%, ESS and FOSQ scores at 12 months relative to baseline. The mean FOSQ score at baseline was 14.3, at the 12-month visit it was 17.2, and at the 18-month visit it was 17.3. The mean ESS score at baseline was 11.6, at the 12-month visit it was 7.0, and at the 18-month it visit was 7.0. The mean percentage of sleep time with SaO2 < 90 at baseline was 8.7%, at the 12-month visit it was 5.9%, and at the 18-month visit it was 5.6%. These results through 18 months show the durability of Inspire therapy's treatment effect.

The randomized controlled therapy withdrawal study provided further evidence that improvements were attributed directly to the Inspire therapy. AHI increased significantly in the therapy withdrawal (OFF) group compared to AHI scores in the therapy maintenance (ON)

group. The results from the randomized control therapy withdrawal study showing the difference between the therapy OFF arm and the therapy ON arm are provided in Table 6.

Table 6. Randomized Controlled Therapy Withdrawal Study Results in Month 13

AHI	Mean AHI		Change (13M–12M) Mean	95% CL for Mean Change	*P value*
	12-Month	13-Month			
Therapy ON	7.2	8.9	1.7	(-1.1, 4.5)	< 0.0001
Therapy OFF	7.6	25.8	18.2	(11.4, 24.9)	

The randomized controlled therapy withdrawal study confirmed that the significant OSA severity reduction at 12 months is attributable to the Upper Airway Stimulation therapeutic effect. An analysis of AHI responder status relative to baseline characteristics is provided in Table 7.

Table 7. AHI Responder Analysis of Baseline Characteristics

Baseline Characteristics	Responders N = 83 Mean % (N)	Non-responders N = 43 Mean % (N)	Association of AHI Response to Baseline Characteristics *P value*
Age	55.9	51.8	0.03
Gender (% Male)	82%	86% (37)	0.56
BMI	28.3	28.6	0.50
Neck Size	41.0	41.6	0.32
Baseline AHI	30.7	34.6	0.08
Baseline ODI	27.1	32.3	0.02
Prior UPPP (%)	20.5% (17)	11.6% (5)	0.22
Baseline FOSQ	14.7	13.6	0.059
Baseline ESS	11.2	12.3	0.22

While the percentage of patients with prior UPPP surgery is noted to be twice as high in the responder group as compared to the non-responder group, the observation was not statistically significant (*P value* of 0.22).

Conclusion

Upper Airway Stimulation is a safe and effective treatment for patients with moderate to severe OSA who are not effectively treated by CPAP.

STAR Clinical Trial Extended Follow Up

Study Objectives
To continue following subjects from the STAR trial in the post-market environment.

Study Design
This was a prospective, single arm cohort study to evaluate the long-term safety of the device in subjects implanted with the Inspire UAS system under the STAR premarket study. The subjects were followed for five years post implant.

Study Population
See the “Patients Studied” Section above in the clinical summary of the STAR trial.

Data Source
The final data in the STAR extended follow-up study through five years post implant.

Key Study Endpoints
See the “Study Design and Methods” Section above in the clinical summary of the STAR trial.

Study Visits and Length of Follow Up
During the premarket phase of the STAR trial all subjects had completed their 18-Month follow up at a minimum. After the 18-Month follow-up visit, subjects continued to be followed long term at 6-month intervals. These long-term follow-ups included adverse event assessment, system interrogation, and therapy titration (as required).

Total Number of Enrolled Study Sites and Subjects’ Follow Up Rate
Of the 126 subjects implanted in the STAR trial, 97 (77%) subjects completed the 60-month final STAR follow-up visit at 18 sites. The final status of the subject follow-up visit compliance is presented in Table 8.

Table 8. Cumulative Implanted Subjects Accountability by Visit

Subjects	Implant	6-	12-	18-	28-	30-	36-	42-	48-	54-	60-
		Month Visit									
Implanted	126	126	126	126	126	126	126	126	126	126	126
Death (Unrelated)	0	0	1	1	2	3	3	3	3	4	5
Withdrawn	0	0	1	1	2	4	7	11	13	15	24
Eligible at Visit	126	126	124	124	122*	119	116	112	110	107	97
Attrition Rate	0	0	1.6%	1.6%	3.2%	5.6%	7.9%	11.1%	12.7%	15.1%	23.0 %
Visit Completed at Interval	126	125	124	123	118	114	110	96	96	90	92

Subjects	Implant	6-	12-	18-	28-	30-	36-	42-	48-	54-	60-
		Month Visit									
Missed Visit	0	1	0	1	4	5	6	16	14	17	5
Missed Visit Rate at Interval	0	0.8%	0	0.8%	3.2%	5.6%	7.9%	14.1%	12.7%	15.9%	5.2%

*One subject had a medically necessary explant unrelated to the Inspire device after the 18-month visit but continued to be followed (post-explant) for safety reasons and exited after completing the 24-month visit.

Safety

Procedure Related Adverse Events (AE)

A majority of the procedure-related events were reported within the first 12 months post-implant. However, a few late experiences of discomfort in the area of incisions or device were reported. One of the later events resulted from inadvertent severing of the stimulation lead during a standard procedure to replace the generator and sensing lead, and thus required replacement of the entire system. All other late-reported events were minor and resolved with medication or no intervention, except for one report of a recurrent cyst at the sensor lead incision site, which eventually resolved without sequelae. Procedure-related non-serious AE's through the 60-month follow up are presented in Table 9.

Table 9. Procedure Related Adverse Events through the 60-Month Follow Up

Adverse Event	Total		Fully Resolved		Partially Resolved		Ongoing	
	# Events	% (# of Subjects)	N	% of Total	N	% of Total	N	% of Total
Events specifically related to an incision	52	30.2% (38)	47	90.4%	5	9.6%	0	0.0%
Post-operative discomfort independent of any surgical incision	42	27.0% (34)	40	95.2%	2	4.8%	0	0.0%
Acute tongue weakness	34	18.3% (23)	32	94.1%	2	5.9%	0	0.0%
Intubation Effects	18	11.9% (15)	18	100.0%	0	0.0%	0	0.0%
Headache	8	6.3% (8)	8	100.0%	0	0.0	0	0.0%

Adverse Event	Total		Fully Resolved		Partially Resolved		Ongoing	
	# Events	% (# of Subjects)	N	% of Total	N	% of Total	N	% of Total
Other post-op symptoms (such as gastrointestinal nausea, vomiting, abdominal pain, constipation), body pain (back, knee, wrist, hand), allergy to antibiotics, anxiety, ineffective airway clearance, loss of some taste, inability to void.	22	11.1% (14)	22	100.0%	0	0.0%	0	0.0%
Infection (mild or moderate)	1	0.8% (1)	1	100.0%	0	0.0%	0	0.0%

Device Related Adverse Events (AE)

Device related events include those resulting from the presence of the device, or delivery of and/or response to the therapy. Most device related events were reported in the first 1-2 years after therapy activation. During this time frame subjects are acclimating to the therapy as optimal settings are established. Of the device-related events reported after the 36-month follow-up, 21 (34%) were classified as temporary external device usability or functionality complaints, which are intended to describe functional issues with the external component operation. These were most often issues with patient remote functioning and were generally resolved with retraining on, or replacement of, the patient programmer. There were also 12 reports (27%) of discomfort due to electrical stimulation which were generally resolved either with adjustments in programming or required no intervention. Device-related non-serious AE's through the 60-month follow up are presented in Table 10.

Table 10. Device-related Non-serious AE's through 60-Month Follow Up

Adverse Event	Total		Fully Resolved		Partially Resolved/ Death		Fully Resolved/ Exit	
	# Events	% (# of Subjects)	N	% of Total	N	% of Total	N	% of Total
Discomfort due to electrical stimulation	142	60.3% (76)	120	84.5%	17	12.0%	5	3.5%
Tongue abrasion	49	27.0% (34)	42	85.7%	4	8.2%	3	6.1%
Mouth dryness	20	15.1% (19)	7	35.0%	9	45.0%	4	20.0%

Adverse Event	Total		Fully Resolved		Partially Resolved/ Death		Fully Resolved/ Exit	
	# Events	% (# of Subjects)	N	% of Total	N	% of Total	N	% of Total
Mechanical pain associated with presence of the device	14	11.1% (14)	9	64.3%	4	28.6%	1	7.1%
Temporary Internal Device Usability or Functionality Compliant	25	16.7% (21)	19	76.0%	5	20.0%	1	4.0%
Temporary External Device Usability or Functionality Complaint	45	26.2% (33)	45	100.0%	0	0.0%	0	0.0%
Other acute symptoms*	39	24.6% (31)	26	66.7%	12	30.8%	1	2.6%
Infection (mild or moderate)	1	0.8% (1)	1	100.0%	0	0.0%	0	0.0%

*Other acute symptoms include miscellaneous reports attributed to the system; for example instances of morning headache, face/neck ache or soreness, insomnia/fatigue, coughing/ choking, and minor dysphasia, tongue deviation or speech related events.

Serious Adverse Events (SAE)

During the five-year follow-up period in the STAR pivotal trial there were nine related serious adverse events (SAE) in eight (6%) of the patients. All SAE's involved a revision/repositioning or replacement of the Inspire system or component(s) of the Inspire system. One revision occurred during the first 12 months of follow-up, and four additional revisions were required during the 12- to 60-month follow-up period. One revision was to reposition the stimulation lead to improve therapy effectiveness, and the others were to address patient discomfort. During the last two years of follow-up four subjects required replacement of the system or a component(s) of the system to address device performance issues in order to improve or restore therapy. The revision and replacement surgeries were without complications or significant sequelae. In addition, one patient had their system explanted due to concerns over a serious infection in their sternoclavicular joint, however upon explant it was determined that there were no signs of infection around the Inspire system components.

Efficacy

Although not required by the long term follow up phase of the protocol, the collection of AHI and ODI measurements was permitted and these objective measures of OSA severity were collected on a majority of patients. The long-term results were consistent with those of the premarket pivotal trial thereby demonstrating a durable therapeutic effect. The baseline, 12-month, 36-month, and 60-month AHI and ODI results are presented in Table 11.

Table 11. Long Term AHI and ODI Results

Outcome Measure	Baseline N Mean ± SD Median	Month 12 N Mean ± SD Median	Month 36 N Mean ± SD Median	Month 60 N Mean ± SD Median
AHI	126 32.0 ± 11.8 29.3	124 15.3 ± 16.1 9.0	98 11.5 ± 14.0 6.0	71 12.4 ± 16.3 6.2
ODI (4%)	126 28.9 ± 18.2 25.4	124 14.0 ± 15.6 7.4	98 9.1 ± 11.7 4.8	71 9.9 ± 14.5 4.6

As was the case in the STAR pivotal trial, the Functional Outcomes Sleep Questionnaire (FOSQ) and Epworth Sleepiness Scale (ESS) results continued to show significant improvement in the subjects' quality of life throughout long term follow up. These validated instruments are commonly used in clinical evaluation and management of OSA. The FOSQ Scores range from 5 to 20, with higher scores indicating greater functioning. A FOSQ score greater than 17.9 is considered to be the cut point for subjects free of any sleep disorders. A change of two or more points in the FOSQ score is a clinically meaningful improvement in daily functioning. The results measured during long-term follow-up compared to baseline are presented in Table 12.

Table 12. Functional Outcomes of Sleep Questionnaire

FOSQ and Change from Baseline by Visit		
Visit	**FOSQ** **(N) Mean ± SD** **Median (Min, Max)**	**Change from Baseline** **(N) Mean ± SD** **Median (Min, Max)**
Month 24	(111) 17.5 ± 2.8 18.6 (6.5, 20.0)	(111) -3.0 ± 3.0 -2.8 (-11.9, 3.2)
Month 30	(112) 17.6 ± 2.7 18.3 (5.0, 20.0)	(112) -3.1 ± 3.3 -2.7 (-12.1, 9.6)
Month 36	(113) 17.3 ± 3.5 18.8 (5.7, 20.0)	(113) -2.7 ± 3.8 -2.6 (-12.7, 10.1)
Month 48	(94) 17.6 ± 2.7 18.8 (6.4, 20.0)	(94) -3.0 ± 3.6 -2.6 (-12.1, 9.0)
Month 54	(90) 17.7 ± 3.1 18.8 (5.4, 20.0)	(90) -2.9 ± 3.7 -3.1 (-10.7, 9.4)
Month 60	(92) 18.0 ± 2.2 18.7 (8.5, 20.0)	(92) -3.2 ± 2.9 -3.1(-12.1, 3.4)

The ESS rates a subject's daytime sleepiness with scores ranging from 0 to 24, lower scores indicating greater functioning. An ESS score of less than 10 is the cut point for normal subjective sleepiness. The results measured in STAR at annual follow-ups compared to baseline are presented in Table 13.

Table 13. Epworth Sleepiness Scale

ESS and Change from Baseline by Visit		
Visit	**FOSQ (N) Mean ± SD Median (Min, Max)**	**Change from Baseline (N) Mean ± SD Median (Min, Max)**
Month 24	(111) 17.5 ± 2.8 18.6 (6.5, 20.0)	(111) -3.0 ± 3.0 -2.8 (-11.9, 3.2)
Month 30	(112) 17.6 ± 2.7 18.3 (5.0, 20.0)	(112) -3.1 ± 3.3 -2.7 (-12.1, 9.6)
Month 36	(113) 17.3 ± 3.5 18.8 (5.7, 20.0)	(113) -2.7 ± 3.8 -2.6 (-12.7, 10.1)
Month 48	(94) 17.6 ± 2.7 18.8 (6.4, 20.0)	(94) -3.0 ± 3.6 -2.6 (-12.1, 9.0)
Month 54	(90) 17.7 ± 3.1 18.8 (5.4, 20.0)	(90) -2.9 ± 3.7 -3.1 (-10.7, 9.4)
Month 60	(92) 18.0 ± 2.2 18.7 (8.5, 20.0)	(92) -3.2 ± 2.9 -3.1(-12.1, 3.4)

Study Strengths and Weaknesses

The follow up rate was quite high during the premarket phase of the study with 124 out of 126 patients completing the primary endpoint follow up. However, during long term follow up in the post market phase of the study the follow up rate dropped to 76.9% (i.e. 97 out of 126 patients).

Conclusion

The STAR trial exceeded all primary and secondary efficacy endpoints, providing the majority of subjects with clinically significant reductions in OSA severity and meaningful improvements in quality of life. The long-term follow up visits through 60 months further demonstrated that Inspire's therapeutic effects are durable and robust.

Pediatric Extrapolation

Existing adult clinical data was leveraged to support Inspire therapy in the pediatric sub-population of adolescents age 18 to 21. There is no data to support use of Inspire UAS in a general pediatric population less than 18 years old. Additionally, published literature data[1,2,3,4,5] indicates there may be a significant chance for spontaneous remission of OSA in pediatric patients who are still growing and may experience changes to their airway and disease characteristics.

References:

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5.Chervin RD, Ellenberg SS, Hou X, et al. Prognosis for Spontaneous Resolution of OSA in Children. *Chest.* 2015; 148(5):1204-1213. doi:10.1378/chest.14-2873

Pediatric OSA Patients with Down Syndrome

An independent physician sponsored study was conducted on 42 pediatric subjects with Down syndrome and severe OSA (i.e., AHI>10) to assess the safety and effectiveness of Inspire therapy in this population. The mean age of the subjects was 15 (standard deviation (SD) of 3.0).

The study subjects had a mean decrease in AHI of 12.9 (SD13.2) at 12 months post implant, and 30 subjects had an AHI<10. These subjects also experienced significant improvements in quality of life with OSA-18 scores improving by a mean of 1.8 points (SD1.2), and ESS scores improving by a mean of 5.1 points (SD6.9).

The most common adverse event was temporary tongue or oral discomfort which occurred in 5 subjects. Four (4) subjects had device or surgery related readmissions due to adverse events such as device extrusion and surgical site infection. No adverse events led to permanent injury or life threatening illness.

Mean therapy usage was 9.0 hours per night (SD1.8).

Reference:

Yu et al. Evaluation of Upper Airway Stimulation for Adolescents with Down Syndrome and Obstructive Sleep Apnea; *JAMA Otolaryngol Head Neck Surg.* 2022; 148(6):522-528

ADHERE Registry Study

Retrospective Analysis of High AHI and High BMI Patients

Study Objective

ADHERE is an ongoing, international, multicenter, observational registry designed to capture outcomes of 5,000 patients implanted with the Inspire Upper Airway Stimulation (UAS) System. A retrospective analysis was conducted on a subset of these patients to evaluate the safety and effectiveness of Inspire UAS in obstructive sleep apnea patients (OSA) patients with baseline AHI scores greater than 65 and less than or equal to 100, and with BMI levels above 32 and less than or equal to 40. The results for these patients were compared to those of patients meeting the STAR pivotal trial's patient selection criteria, i.e., those with AHI scores of 65 or less, and with BMI levels less than or equal to 32.

Study Population

The retrospective analysis of the AHI subgroups included 1,483 patients with a baseline (pretreatment) AHI≤65; 31 patients with a baseline AHI between 65 and 75; 26 patients with a baseline AHI between 75 and 100. The analysis of the BMI subgroups included 1,218 patients with a BM≤32; and 279 with BMI≤40.

Data Analysis

Patients in the AHI and BMI subgroups had a final follow up visit with at least one of the following values recorded at that final visit: AHI, ESS, Therapy Usage, CGI (Clinical Global Impression), and/or Patient Satisfaction data.

Safety

AHI Groups

As shown in the following table, when comparing events that occurred during the implant procedure for the AHI groups (AHI≤65, 65<AHI≤75, and 75<AHI≤100) there was no difference in the rate of serious or non-serious implant adverse events.

Table 14. Implant Adverse Events by Seriousness and Baseline AHI

Implant AEs	AH≤65 (N = 3572)		65<AHI≤75 (N = 65)		75<AHI≤100 (N = 58)		*P value**
	Total Events	Subject with Events	Total Events	Subject with Events	Total Events	Subject with Events	
Total	151	131 (3.7%)	1	1 (1.5%)	3	2 (3.4%)	0.85
Serious	24	24 (0.7%)	0	0 (0%)	0	0 (0%)	
Nonserious	125	105 (2.9%)	1	1 (1.5%)	3	2 (3.4%)	

Note: Format for Subjects with Events: Number of subjects with at least one event (% of subjects per AHI group); **P value* derived from Fisher's exact test.

In addition, there was no difference in the rate of serious or non-serious follow-up adverse events for the AHI groups.

Table 15. Follow-up Adverse Events by Seriousness and Baseline AHI

Implant AEs	AH≤65 (N = 1483)		65<AHI≤75 (N = 31)		75<AHI≤100 (N = 26)		*P value**
	Total Events	Subject with Events	Total Events	Subject with Events	Total Events	Subject with Events	
Total	550	432 (29.1%)	18	13 (41.9%)	13	8 (30.8%)	
Serious	44	42 (2.8%)	1	1(3.2%)	0	0 (0%)	0.28
Nonserious	503	399 (26.9%)	17	12 (38.7%)	13	8 (30.8%)	

Note: Format for Subjects with Events: Number of subjects with at least one event (% of subjects per AHI group); Subjects could have had more than one follow-up event; **P value* derived from Fisher's exact test e*xcluding unrelated adverse events.*

Table 16. Procedure-related Adverse Events by Characteristics and Baseline AHI

Characteristics	AH≤65 (N = 3752)	65 < AHI≤100 (N=123)
	Subjects with Events	Subject with Events
Serious Adverse Events		
Total	**24 (0.7%)**	**0 (0%)**
Revisions	13 (0.4%)	0 (0%)
Tachycardia	2 (0.1%)	0 (0%)
Pneumothorax	1 (0.03%)	0 (0%)
Infection	1 (0.03%)	0 (0%)
Hematoma	1 (0.03%)	0 (0%)
Hypotension	1 (0.03%)	0 (0%)
Rhabdomyolysis	1 (0.03%)	0 (0%)
Intraoperative Arrest/Bradycardia	1 (0.03%)	0 (0%)
Cervical Swelling with Submandibular Hematoma	1 (0.03%)	0 (0%)
Chest Pain with Tachycardia	1 (0.03%)	0 (0%)
Bradycardia	1 (0.03%)	0 (0%)
Non-Serious Adverse Events		
Total	**105 (2.9%)**	**3 (2.4%)**
Hematoma	14 (0.4%)	0 (0%)
Intraoperative Bleeding	10 (0.3%)	0 (0%)
Speech Difficulties	7 (0.2%)	1 (0.8%)
Headache	6 (0.2%)	1 (0.8%)
Tongue Weakness	6 (0.2%)	1 (0.8%)
Incision Discomfort/Irritation	5 (0.1%)	0 (0%)
Pneumothorax	5 (0.1%)	0 (0%)
Neuropraxia	5 (0.1%)	0 (0%)
Tongue Discomfort/Irritation	4 (0.1%)	0 (0%)
Chest Pain	4 (0.1%)	0 (0%)
Seroma	4 (0.1%)	0 (0%)
Infection	3 (0.1%)	1 (0.8%)
Lip Weakness	3 (0.1%)	0 (0%)

Characteristics	AH≤65 (N = 3752)	65 < AHI≤100 (N=123)
	Subjects with Events	Subject with Events
Postoperative Bleeding	3 (0.1%)	0 (0%)
Ecchymosis	3 (0.1%)	0 (0%)
Edema	3 (0.1%)	0 (0%)
Facial Swelling	3 (0.1%)	0 (0%)
Nerve Weakness	2 (0.1%)	0 (0%)
Urinary Retention	2 (0.1%)	0 (0%)
Tongue Deviation	2 (0.1%)	0 (0%)
Sore Throat	2 (0.1%)	0 (0%)
Postoperative Desaturation	2 (0.1%)	0 (0%)
Atrial Fibrillation	2 (0.1%)	0 (0%)
Intraoperative Nerve Repositioning	1 (0.03%)	0 (0%)
Cuff Placement Challenges	1 (0.03%)	0 (0%)
Discomfort - Swallowing	1 (0.03%)	0 (0%)
Allergic Reaction at Incision Site	1 (0.03%)	0 (0%)
Tongue Movement Change	1 (0.03%)	0 (0%)
Neck Pain	1 (0.03%)	0 (0%)
Difficult Dissection	1 (0.03%)	0 (0%)
IPG Reposition	1 (0.03%)	0 (0%)
Conversion Disorder	1 (0.03%)	0 (0%)
Cervical Swelling	1 (0.03%)	0 (0%)
Eye Pain	1 (0.03%)	0 (0%)
Technical Challenges	1 (0.03%)	0 (0%)
Dysphagia	1 (0.03%)	0 (0%)
Wound Dehiscence	1 (0.03%)	0 (0%)
Discomfort - IPG	1 (0.03%)	0 (0%)
Neck Swelling	1 (0.03%)	0 (0%)
Bradycardia	1 (0.03%)	0 (0%)
Incision Swelling	1 (0.03%)	0 (0%)
Mouth Pain	1 (0.03%)	0 (0%)
Nerve Damage	1 (0.03%)	0 (0%)
Hypotension	1 (0.03%)	0 (0%)

Table 17. Follow-up Adverse Events by Characteristics and Baseline AHI

Characteristics	AH≤65 (N = 1483)	65 < AHI≤100 (N=57)
	Subjects with Events	Subject with Events (continued)
Serious Adverse Events		
Total	**42 (2.8%)**	**1 (1.8%)**
Revisions	38 (2.6%)	1 (1.8%)
Swallowing, Chewing, and Talking Not Possible Immediately After Surgery	1 (0.1%)	0 (0%)
Sore Tongue, Difficulty Talking While Inspire is Off and Attacking Pain in Left Lower Jaw	1 (0.1%)	0 (0%)
System Explant	1 (0.1%)	0 (0%)
Unspecified	1 (0.1%)	0 (0%)
Non-Serious Adverse Events		
Total	**404 (27.2%)**	**20 (35.0%)**
Stimulation-related Discomfort	181 (12.2%)	11 (19.3%)
Other Device/Therapy-related Event	81 (5.5%)	2 (3.5%)
Insomnia/Arousal	80 (5.4%)	8 (14.0%)
Discomfort (Incision/Scar)	64 (4.3%)	0 (0%)
Other Discomfort	61 (4.1%)	4 (7.0%)
Tongue Abrasion	43 (2.9%)	3 (5.3%)
Other Procedure-related Event	41 (2.8%)	4 (7.0%)
Discomfort (Device)	26 (1.8%)	3 (5.3%)
Swallowing or Speech-related	21 (1.4%)	0 (0%)
Tongue Weakness	10 (0.7%)	0 (0%)
Infection	8 (0.5%)	0 (0%)

BMI Groups

The table below shows that when comparing events that occurred during the implant procedure in the BMI groups (BMI≤32, 32<BMI≤35, and 35<BMI≤40) there was no difference in the rate of events in the BMI<40 groups. In the 35 < BMI ≤ 40 group, there was one report of Rhabdomyolysis, which is an adverse event that had not been seen previously in the STAR trial.

Table 18. Implant Adverse Events by Seriousness and Baseline BMI

Implant AEs	BMI≤32 (N = 2832)		32<AHI≤35 (N = 592)		32<BMI≤40 (N = 156)		*P value**
	Total Events	Subject with Events	Total Events	Subject with Events	Total Events	Subject with Events	
Total	122	105 (3.7%)	21	19 (3.2%)	5	5 (3.2%)	
Serious	19	19 (0.7%)	3	3 (0.5%)	2	2 (1.3%)	9.2e-01
Nonserious	101	84 (3%)	18	16 (2.7%)	3	3 (1.9%)	

Note: Format for Subjects with Events: Number of subjects with at least one event (% of subjects per AHI group); Subjects could have had more than one follow-up event; **P value* derived from Fisher's exact test excluding unrelated adverse events.

The following table shows that when comparing the events that occurred during therapy follow-up for the BMI groups, there was no difference in the rate of serious or non-serious follow-up adverse events.

Table 19. Follow-up Adverse Events by Seriousness and Baseline BMI

Implant AEs	BMI≤32 (N = 1218)		32<AHI≤35 (N = 222)		35<BMI≤40 (N = 57)		*P value**
	Total Events	Subject with Events	Total Events	Subject with Events	Total Events	Subject with Events	
Total	456	351 (28.8%)	86	71 (32%)	25	20 (35.1%)	
Serious	33	32 (2.6%)	8	8 (3.6%)	2	1 (1.8%)	0.48
Nonserious	422	328 (26.9%)	76	63 (28.4%)	23	19 (33.3%)	

Note: Format for Subjects with Events: Number of subjects with at least one event (% of subjects per BMI group); Subjects could have had more than one follow-up event; **P value* derived from Fisher's exact test.

Table 20. Procedure-related Adverse Events by Characteristics and Baseline BMI

Characteristics	BMI ≤ 32 (N=2832)	32 < BMI ≤ 40 (N=748)
	Subjects with Events	Subject with Events
Serious Adverse Events		
Total	19 (0.7%)	5 (0.7%)
Revisions	12 (0.4%)	1 (0.1%)
Tachycardia	2 (0.1%)	0 (0%)
Pneumothorax	1 (0.04%)	0 (0%)
Hypotension	1 (0.04%)	0 (0%)
Intraoperative Arrest/Bradycardia	1 (0.04%)	0 (0%)
Cervical Swelling with Submandibular Hematoma	1 (0.04%)	0 (0%)
Bradycardia	1 (0.04%)	0 (0%)
Infection	0 (0%)	1 (0.1%)
Hematoma	0 (0%)	1 (0.1%)
Rhabdomyolysis	0 (0%)	1 (0.1%)
Chest Pain with Tachycardia	0 (0%)	1 (0.1%)
Non-serious Adverse Events		
Total	84 (3.0%)	19 (2.5%)
Hematoma	12 (0.4%)	2 (0.3%)
Intraoperative Bleeding	9 (0.3%)	1 (0.1%)
Speech Difficulties	8 (0.3%)	0 (0%)
Headache	6 (0.2%)	1 (0.1%)
Tongue Weakness	6 (0.2%)	1 (0.1%)
Pneumothorax	5 (0.2%)	0 (0%)
Infection	4 (0.1%)	1 (0.1%)
Incision Discomfort/Irritation	4 (0.1%)	1 (0.1%)
Neuropraxia	4 (0.1%)	1 (0.1%)
Postoperative Bleeding	3 (0.1%)	0 (0%)

Characteristics	BMI ≤ 32 (N=2832)	32 < BMI ≤ 40 (N=748)
	Subjects with Events	Subject with Events
Seroma	3 (0.1%)	1 (0.1%)
Tongue Discomfort/Irritation	2 (0.1%)	2 (0.3%)
Unknown	2 (0.1%)	2 (0.3%)
Nerve Weakness	2 (0.1%)	0 (0%)
Chest Pain	2 (0.1%)	0 (0%)
Ecchymosis	2 (0.1%)	0 (0%)
Sore Throat	2 (0.1%)	0 (0%)
Atrial Fibrillation	2 (0.1%)	0 (0%)
Lip Weakness	1 (0.04%)	1 (0.1%)
Cuff Placement Challenges	1 (0.04%)	0 (0%)
Discomfort - Swallowing	1 (0.04%)	0 (0%)
Allergic Reaction at Incision Site	1 (0.04%)	0 (0%)
Tongue Movement Change	1 (0.04%)	0 (0%)
Neck Pain	1 (0.04%)	0 (0%)
Urinary Retention	1 (0.04%)	0 (0%)
IPG Reposition	1 (0.04%)	0 (0%)
Conversion Disorder	1 (0.04%)	0 (0%)
Cervical Swelling	1 (0.04%)	0 (0%)
Tongue Deviation	1 (0.04%)	1 (0.1%)
Edema	1 (0.04%)	1 (0.1%)
Facial Swelling	1 (0.04%)	1 (0.1%)
Eye Pain	1 (0.04%)	0 (0%)
Postoperative Desaturation	1 (0.04%)	1 (0.1%)
Technical Challenges	1 (0.04%)	0 (0%)
Discomfort - IPG	1 (0.04%)	0 (0%)
Neck Swelling	1 (0.04%)	0 (0%)
Bradycardia	1 (0.04%)	0 (0%)
Incision Swelling	1 (0.04%)	0 (0%)
Mouth Pain	1 (0.04%)	0 (0%)
Nerve Damage	1 (0.04%)	0 (0%)
Hypotension	1 (0.04%)	0 (0%)
Intraoperative Nerve Repositioning	0 (0%)	1 (0.1%)
Difficult Dissection	0 (0%)	0 (0%)
Dysphagia	0 (0%)	1 (0.1%)
Wound Dehiscence	0 (0%)	1 (0.1%)

Table 21. Follow-up Adverse Events by Characteristics and Baseline BMI

Characteristics	BMI ≤ 32 (N=1218)	32 < BMI ≤40 (N=279)
	Subjects with Events	Subject with Events
Serious Adverse Events		
Total	32 (2.6%)	9 (3.2%)
Revisions	29 (2.4%)	8 (2.9%)
Swallowing, Chewing, and Talking Not Possible Immediately After Surgery	1 (0.08%)	0 (0%)
Sore Tongue, Difficulty Talking While Inspire is Off and Attacking Pain in Left Lower Jaw	1 (0.08%)	0 (0%)
System Explant	1 (0.08%)	0 (0%)
Unspecified	0 (0%)	1 (0.5%)
Non-serious Adverse Events		
Total	331 (27.2%)	84 (30.1%)
Stimulation-related Discomfort	157 (12.9%)	29 (10.4%)
Other Device/Therapy-related Event	69 (5.7%)	12 (4.3%)
Insomnia/Arousal	67 (5.5%)	20 (7.2%)
Discomfort (Incision/Scar)	56 (4.6%)	7 (2.5%)
Other Discomfort	49 (4.0%)	15 (5.4%)
Other Procedure-related Event	36 (3.0%)	9 (3.2%)
Tongue Abrasion	30 (2.5%)	16 (5.7%)
Discomfort (Device)	24 (2.0%)	4 (1.4%)
Swallowing or Speech-related	16 (1.3%)	5 (1.8%)
Tongue Weakness	8 (0.7%)	2 (0.7%)
Infection	6 (0.5%)	2 (0.7%)

Effectiveness

AHI Groups

The patients with a baseline AHI greater than 65 and less than or equal to 100 met the same pre-specified AHI reduction criteria used in the STAR trial to demonstrate the effectiveness of the Inspire UAS. This criterion is known as the Sher criteria (i.e., a 50% reduction in AHI and an AHI < 20). The STAR pivotal trial required a 50% responder rate to that criteria in order to meet the AHI reduction endpoint. The following table shows that all AHI groups in the retrospective analysis of the ADHERE data met that same requirement and furthermore, there was no statistically significant difference in the responder rates of the AHI groups.

ESS scores of 10 or less are considered equivalent to normalized sleep. The analysis here showed that final mean ESS scores were all well below 10 for all AHI groups and that the change from baseline to final ESS for all AHI groups was not statistically different when compared to each other. This analysis is summarized in the following table.

Table 22. AHI Outcomes by Baseline AHI

Variable	AHI ≤ 65	65 < AHI ≤ 75	75 < AHI ≤ 100	*P value**	Type of Test*
Final AHI	15.6 ± 14.8 (11.3), 0 - 96.2, N=1138	20.76 ± 18.18 (16.6), 0.8 - 64.1, N=25	15.23 ± 20.1 (6.25), 0 - 70, N=14	0.19	Kruskal-Wallis Test
Change in AHI - Baseline to Final	18.86 ± 16.89 (18.5), -46.3 - 64.9, N=1138	48.25 ± 18.11 (52.7), 4.8 - 69.9, N=25	66.48 ± 19.1 (72.9), 17 - 92.3, N=14	<0.001	ANOVA
Responder - Sher	64.3% (732)	64% (16)	71.4% (10)	0.93	Fisher's Exact Test
Non-responder - Sher	35.7% (406)	36% (9)	28.6% (4)		
Final ESS	6.88 ± 4.54 (6), 0 - 23, N=1231	6.6 ± 5.07 (6), 1 - 20, N=25	6.05 ± 4.42 (5), 0 - 16, N=20	0.58	Kruskal-Wallis Test
Change in ESS - Baseline to Final	4.53 ± 5.21 (4), -13 - 23, N=1108	3.96 ± 4.74 (4), -3 - 20, N=23	4 ± 5 (4), -6 - 14, N=19	0.80	ANOVA

***Note:** Format for numeric variables: Mean ± SD (Median), Range.*

Usage data from the ADHERE registry also demonstrates that when comparing the AHI groups (AHI≤65, 65<AHI≤75, and 75<AHI≤100) there is no statistical difference in hours of use per night.

Table 23. ESS Outcomes by Baseline AHI

Variable	AHI≤65	65<AHI≤75	75<AHI≤100	*P Value*	Type of Test
Therapy Use at Final Visit	5.74±2.21 (6), [0, 10.29] N=1146	4.93±2.49 (5.14), [0.57, 9] N=23	5.05±2.72 (5.21), [0, 8.71] N=18	0.0981	ANOVA

Note: Format for numeric variables: Mean ± SD (Median), [Range].

BMI Groups

The patients with a baseline BMI greater than 32 meet the pre-specified criteria used in the STAR pivotal trial which demonstrated the effectiveness of Inspire UAS. The analysis also showed that there was no statistical difference in Final ESS or Change in ESS when the different BMI groups were compared with each other. It should be noted that the mean ESS scores for each group are well below 10 which is considered the cut point for normalized sleep. This analysis is summarized in the following table.

Table 24. AHI Outcomes by Baseline BMI (BMI≤32 vs. 32<BMI≤40)

Variable	BMI ≤ 32	32 < BMI ≤ 35	35 < BMI ≤ 40	P value	Type of Test*
Final AHI	15.34 ± 14.44 (10.95), 0 - 83.8, N=930	17.39 ± 16.9 (12.95), 0 - 96.2, N=170	17.01 ± 16.78 (13.35), 0 - 92, N=46	0.24	Kruskal-Wallis Test
Change in AHI - Baseline to Final	20.09 ± 18.11 (19.25), -41.6 - 92.3, N=930	21.15 ± 20.13 (19.95), -46.3 - 103.2, N=170	18.43 ± 17.46 (18), -27.5 - 56.2, N=46	0.64	ANOVA
Responder - Sher	65.1% (605)	60.6% (103)	60.9% (28)	0.47	Fisher's Exact Test
Non-responder - Sher	34.9% (325)	39.4% (67)	39.1% (18)		
Final ESS	6.87 ± 4.57 (6), 0 - 23, N=1012	6.76 ± 4.53 (6), 0 - 22, N=186	6.94 ± 4.59 (6.5), 0 - 17, N=50	0.93	Kruskal-Wallis Test
Change in ESS - Baseline to Final	4.59 ± 5.08 (4), -13 - 23, N=906	4.48 ± 5.98 (4.5), -13 - 19, N=170	3.6 ± 5 (3), -6 - 17, N=47	0.44	ANOVA

Note: Format for numeric variables: Mean ± SD (Median), Range.

Usage data from the ADHERE registry also demonstrates that when comparing the BMI groups there was a statistical difference in hours of use per night. Patients with BMI > 32 use their device 45 minutes less per night on average than patients with BM ≤ 32. However, all BMI groups exceeded the therapy usage threshold for CPAP compliance which is 4 hours of use per night for 5 nights per week.

Table 25. Therapy Use at Final Visit by Baseline BMI (BMI≤32 vs. 32<BMI≤35 vs. BMI>35)

Variable	BMI≤32	32<BMI≤35	BMI<35	*P Value*	Type of Test
Therapy Use at Final Visit	5.86±2.2 (6.14), [0, 10.29] N=937	5.19±2.36 (5.29), [0, 10] N=176	4.89±2.09 (5.14), [0, 9.29] N=57	2e-05	ANOVA

Note: Format for numeric variables: Mean ± SD (Median), [Range].

Conclusion

The STAR trial, which studied patients with AHI Scores ranging from 15 to 65 and with BMI scores of 32 or less, exceeded all primary and secondary efficacy endpoints, providing the majority of subjects with clinically significant reductions in OSA severity and meaningful improvements in quality of life. The retrospective analysis of the ADHERE registry data included patients with AHI scores greater than 65 and up to 100, and BMI scores ranging from greater than 32 up to and including 40. The results of that analysis demonstrates that Inspire UAS provides higher AHI and BMI patients with a favorable safety profile, AHI reduction, and quality of life improvements similar to those experienced by the STAR trial patients.

Generator Specifications

Factory Settings

Table 26. Inspire 3150 Implantable Pulse Generator Factory Settings

Parameter	Value
General	
Therapy On/Off	Off
Usage	0
Stimulation	
Amplitude	0V
Output Rate	33 Hz
Pulse Width	90 µs
Patient Control	Off
Electrode Configuration	A [+ - +] (o)
Start Delay	30 minutes
Pause Time	15 minutes
Therapy Duration	8 hours
Ramp	0 minutes
Start Impulse	100%
Step Size	0.1 V
Sensing	
Exhalation Sensitivity	-4
Exhalation Threshold	-1
Inhalation Sensitivity	0
Inhalation Threshold	+1
Hard Refractory	38%
Soft Refractory	13%
Invert Signal	Off
Max Stim Time	4 seconds

Configurable Settings

The parameters in Table 27 can be changed using an Inspire programmer. See the physician programmer manual for more information.

Table 27. Inspire 3150 Implantable Pulse Generator Configurable Settings

Parameter	Values	Increment
General		
Therapy On/Off	Off	
Usage	0	
Stimulation		
Amplitude	0.00-5.00 V	0.1 V, 0.05 V, 0.025 V
Output Rate	30, 33, 40 Hz	
Pulse Width	60, 90, 120, 150, 180, 210 µs	
Patient Control	On, Off	
Electrode Configuration	A [+ - +] (o) E [- + -] (o) D [- - -] (+) B [o - o] (+) C [- o -] (+)	(+), (-), (o) (-), (+), (o) (-), (-), (+) (o), (-), (+) (-), (o), (+)
Start Delay	0–60 minutes	5 minutes
Pause Time	5–30 minutes	5 minutes
Therapy Duration	1–15 hours	1 hour
Ramp	0, 5, 10, 15 minutes	
Start Impulse	100%, 90%, and 80%	
Step Size	0.1 V, 0.05 V, 0.025 V	
Sensing		
Exhalation Sensitivity	-4 to +3	1
Exhalation Threshold	-1 to +1	1
Inhalation Sensitivity	-7 to 0	1
Inhalation Threshold	0 to +1	1
Hard Refractory	38, 50, 63, 75%	
Soft Refractory	13, 25%	
Invert Signal	On, Off	
Max Stim Time	2–5 seconds	1.0 seconds

Battery Longevity

Longevity Estimate 10.9 years average[a]
End of Service[c] 1 month after Recommended Replacement Time[b]

(a) Generator longevity will vary based on usage and therapy settings. The minimum estimated longevity is 7 years.
(b) Recommended Replacement Time - The sleep remote generator light turns on to indicate that replacement of the Model 3150 is recommended within 1 month.
(c) End of Service - The Model 3150 should be replaced immediately.

Physical Description

Table 28. Inspire 3150 Generator Physical Description

Description	Value
Height	46 mm (1.8 in)
Length	51 mm (2.0 in)
Thickness	8.4 mm (0.33 in)
Volume	15c m^3 (0.92 in^3)
Radiopaque identification	IMSV
Tissue contacting materials	Titanium, polyurethane, silicone rubber

Radiopaque identification
The generator's radiopaque identification, IMSV (Figure 14), can be confirmed by using fluoroscopy on the generator.

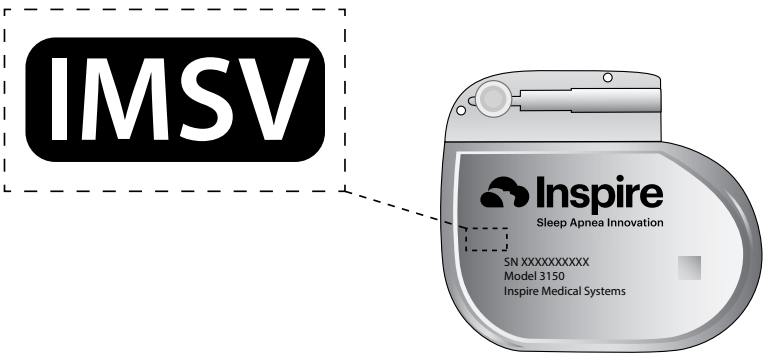

Figure 14. *Radiopaque identification*

Inspire Medical Systems Limited Warranty

Summary

Inspire provides a limited warranty against defects. The warranty period for implanted products is 3 years. All other products have a warranty period of 1 year.

The warranty information below is intended for doctors (referred to as physicians in the warranty), but is included here for reference. Ask your doctor if you have any questions. The information below takes precedence over the information contained in this Summary.

Inspire Medical Systems' products consist of generators, tools to connect the generator to implantable leads, leads, Inspire Sleep Remotes, and physician programmers.

1. **EXCLUSION OF WARRANTIES, NO WARRANTIES FOR TOOLS.** The implied warranties of MERCHANTABILITY and fitness for a particular purpose and all other warranties, express or implied with regard to tools are EXCLUDED from any transaction and shall not apply. Inspire Medical Systems will not be liable for any damages, whether direct, consequential, or incidental caused by tool defects, failures, or malfunctions, whether such claims are based on warranty, contract, tort or otherwise. No person has any authority to bind Inspire Medical Systems to any representation or warranty with respect to tools. You may have other rights, which vary from state to state. If one or more of the provisions of this exclusion of warranties for tools shall be deemed void or unenforceable, the remaining provisions shall continue to have full force and effect.
2. **LIMITED WARRANTY FOR PRODUCTS OTHER THAN TOOLS.** This limited warranty is available if products other than tools fail to function within normal tolerances due to defects in materials or workmanship that manifest during the specified warranty period.

During the operational life of an generator, battery energy is consumed to monitor the patient's breathing and provide therapy. On the basis of individual patient physiology, certain patients may require more frequent therapy, thus requiring replacement of the generator in less than the warranty period shown below. This is considered normal for those patients and not a malfunction or defect in the generator.

If the purchaser complies with the Terms and Conditions, Inspire Medical Systems will issue a limited warranty toward the purchase of a new Inspire Medical Systems generator product. The limited warranty credit amount will be the full purchase price of either the original unit or the replacement unit, whichever is less.

- For patient products, for example, generator, lead, Inspire Sleep Remote, Inspire Medical Systems will issue a credit to the hospital conducting replacement surgery on behalf of the original patient. Any cost reductions extended as a result of this warranty shall be fully and accurately reflected on the patients' bill and reported to that applicable payor using the appropriate methodology.
- For physician products, for example, physician programmer, Inspire Medical Systems will issue a credit to the original purchaser of the product.

A. Terms and Conditions

1. The product labeling must indicate a limited warranty exists.
2. For implantable products, this limited warranty applies only for a product replacement in the original patient.
3. All registration materials must be completed and returned to Inspire Medical Systems within 30 days of first use.
4. The product must be replaced with an Inspire Medical Systems product.
5. If the product is implantable, it must be implanted before the product expires and implanted with other Inspire Medical Systems products.
6. The product must be returned to Inspire Medical Systems, 5500 Wayzata Blvd, Suite 1600, Golden Valley, MN 55416 within 30 days that the product first fails to function within normal tolerances. The product may be returned at no cost to you. Contact your Inspire Medical Systems representative for information on how to return the product.
7. Inspire Medical Systems will inspect the returned product and determine whether a limited warranty credit is due.
8. All products returned to Inspire Medical Systems become its property.

This limited warranty represents the entire obligation of Inspire Medical Systems for products other than tools and is made IN LIEU OF any other warranties, whether express or implied, including MERCHANTABILITY or fitness for a particular purpose.

Inspire Medical Systems will not be liable for any damages, whether direct, consequential, or incidental caused by product defects, failures, or malfunctions, whether such claims are based on warranty, contract, tort or otherwise.

No person has any authority to bind Inspire Medical Systems to any warranty or representation except those specifically contained herein.

This limited warranty gives specific legal rights, and you may also have other rights, which vary from state to state. If one or more of the provisions of this limited warranty shall be deemed void or unenforceable, the remaining provisions shall continue to have full force and effect.

B. Limited Warranty Period

The applicable limited warranty period for each product is listed and calculated as follows:

1. Three (3) years from date an generator or lead is implanted in the patient.
2. One (1) year from the date a physician programmer or Inspire Sleep Remote is first used.

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