NeuRx Diaphragm Pacing System™
Surgeon Instruction Manual

SYNAPSE
Biomedical Inc.

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1.0 GENERAL OVERVIEW

This technique guide is designed as a supplement, not as a substitute, for proctorship by a certified surgeon experienced in placement of the NeuRx® Diaphragm Pacing System (NeuRx DPS®). It is not intended as a standalone document.

The purpose of this guide is to establish clinical guidelines and practices to successfully apply the required processes to surgically implant, condition and manage a patient with the NeuRx DPS from the clinical aspect.

The procedure and technique guide is not intended as a standalone document. The additional instructions of other Synapse Biomedical manuals will add clinical support and training as necessary.

2.0 INDICATIONS FOR USE

The NeuRx® Diaphragm Pacing System (NeuRx DPS®) is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but lack control of their diaphragms. The device is indicated to allow patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. For use in patients 18 years of age or older.

Caution: Federal Law (USA) restricts this device to sale, distribution and use by or on the order of a physician.

3.0 Symbol Descriptions

The ***Warning*** symbol precedes warning information that mitigates a risk that is not obvious to the operator. Indicates that a potentially hazardous situation which, if not avoided, could result in harm to the operator or patient.

The ***Warning*** symbol on powered equipment indicates physiological effects not obvious to the user that can cause harm.

Y The ***Caution*** symbol appears next to precautionary information when the intention is solely to inform. Indicates that a potentially hazardous situation which, if not avoided, may result in minor or moderate personal injury or property damage. This word is used to also alert against unsafe practices.

M The ***Manufacturer*** symbol appears next to the manufacturer's name and address.

h The ***Reference*** symbol appears preceding the part number for the device. The part number is a unique numeric identifier for the device.

g The ***Lot*** symbol appears preceding the lot number for a device. Devices manufactured at the same time using identical material and parts will share a common lot number.

f The ***Serial Number*** symbol appears on devices that require unique identification.

H The ***Use Until*** symbol appears on devices that have an indication of the date by which the device should be used. The date is expressed as the year and month, with the month referring to the end of the month.

I The ***Temperature Limits*** symbol appears on packages of devices/components as an indication of the storage temperature limits.

p The ***Keep Dry*** symbol appears on all packages of devices requiring to protect the packaging from potential damage.

L The ***Don't Use If Packing Damaged*** symbol appears on all packages of devices requiring to dispose of the device if the packaging has suffered damage.

i The ***Accompanying Documents*** symbol appears on all packages of devices indicating that instructions for use are available for additional information.

C2797 The ***Regulatory Marking of Conformity*** symbol indicates that the device meets Medical Device Directive 93/42/EEC. This has been certified by notified body number 2797.

P The ***European Community Representative*** symbol indicates the identification of the authorized representative for the distribution of devices into the European community.

The ***Type BF Applied Part*** symbol appears on powered equipment that connects directly to a patient. It is an indication of the degree of protection provided against electric shock, patient leakage current and patient auxiliary current.

The ***On / Off*** symbol on powered equipment indicates push-button ON/OFF power control of the device.

The ***Consult Accompanying Documents*** symbol appears on powered equipment indicating that instructions for use must be consulted for safety.

The ***MR Unsafe*** symbol. A device that is known to pose hazards in all MR environments

Gamma Sterilization. This simple, proven process is safe, reliable, and highly effective at treating single-use medical devices. With the ability to penetrate products while sealed in their final packaging, gamma irradiation supports the manufacturing and distribution process by facilitating final packaged product as well as raw materials, whilst still ensuring full sterility of the product.

The ***Sterile Medical Device By Ethylene Oxide*** symbol indicates the Device has been Sterilized By Ethylene Oxide.

This symbol indicates that the item is for **single use only** and must not be used more than once.

This symbol indicates that the device should not be re-sterilized after it once has been sterilized.

This symbol indicates **two sterile barrier** systems.

This symbol indicates a **single sterile barrier** system with protective packaging outside.

This symbol indicates the item is a **medical device**.

This symbol indicates the **range of humidity** to which the medical device can be safely exposed.

This symbol indicates the **range of atmospheric pressure** to which the medical device can be safely exposed.

This symbol indicates a carrier that contains **unique device identifier** information.

This symbol indicates the **country of manufacture** of products. The ***Manufactured Date*** symbol appears on devices as an indication of the date of manufacture. The date is expressed as the year and month.

This symbol indicates biological substances that pose a threat to the health of living organisms, primarily that of humans.

4.0 WARNINGS AND CAUTIONS

- Spinal Cord Injury (SCI) patients must have a mechanical ventilator available at all times. If the patient does not feel that they are receiving adequate ventilation or if any malfunction of the pacing device is suspected, they should be placed on mechanical ventilation immediately and the pacing system turned off. Caregiver availability and monitoring should be consistent with when a ventilator is used.
- **WARNING:** NeuRx DPS could interfere with some medical equipment. Some medical equipment could interfere with the NeuRx DPS. Call your healthcare provider who is helping you with your NeuRx DPS before having any of the following:
  - **Active implantable medical devices**. The use of the NeuRx® External Pulse Generator (NeuRx® EPG) stimulator may interfere with active implantable medical devices. This includes devices such as implanted cardiac pacemakers, implanted cardioverter defibrillators (ICDs), implanted neurostimulators, and body worn medical devices (e.g., insulin pump). There is not enough information to know for sure whether the NeuRx DPS® can be used safely with these devices. Please consult with a specialist and perform device-to-device interaction testing to establish compatibility.
  - **Surgery**. Use of high-frequency surgical equipment may cause burns where the electrode wires pass through the skin. It might also damage the NeuRx EPG if connected.
  - **Magnetic Resonance Imaging (MRI) test.** The PermaLoc electrode is MR Unsafe. Do not perform a MRI test while implanted with the PermaLoc electrodes.
  - **Magnetic Resonance Imaging (MRI) test.** The NeuRx EPG stimulator and surface electrodes are MR Unsafe. The NeuRx DPS has not been tested with MRI. MRI could cause the electrode wires to move. MRI could also cause unwanted tissue heating through the electrode wires.
  - **Diathermy treatment.** Diathermy treatment is deep tissue heat treatment. It should not be performed within 30cm of the implanted electrode leads. Unwanted tissue heating through the electrode wires could occur.
  - **External electrical stimulation** such as **transcutaneous electrical nerve stimulation (TENS).** Such stimulation should not be done in the chest area near the electrode wires. Unwanted diaphragm contraction could occur.
  - **Shortwave or microwave therapy.** Operating the NeuRx DPS close to (about 3 feet from) such equipment may interfere with the NeuRx DPS.

- **WARNING:** This device is electrically powered and may produce tissue damage or electrical hazard if improperly used.

- **WARNING:** This device should be kept out of the reach of children.

- **WARNING:** Do NOT implant the NeuRx DPS if the patient is pregnant or is planning on getting pregnant. It is not known if it is safe to use the NeuRx DPS in pregnant women.

- **WARNING:** Patients should avoid eating or drinking with initial conditioning with the NeuRx DPS. There is a risk of food or liquid entering the lungs.

- **WARNING:** Do NOT attempt to open the NeuRx EPG case. Doing so can result in damage to the device.

- **WARNING:** Do NOT use this device if skin in the electrode implant area is swollen, infected, or inflamed.

- **WARNING:**  STERILE EO
Sterile components that are double pouched, the primary sterile barrier is the inner pouch. The outer pouch is considered a secondary barrier for the inner pouch. Visually inspect all STERILE barriers before use. Do NOT use the device if the sterile barrier is open, damaged or broken.

- **WARNING:**  STERILE R
Sterile components are sealed in a sterile tray and placed into a protective outer package. The sealed sterile tray is a sterile barrier. The protective outer package is not a considered a sterile barrier. Visually inspect all STERILE barriers before use. Do NOT use the device if the sterile barrier is open, damaged or broken.

5.0 FLAMMABILITY WARNING ⚠

- Do NOT use the NeuRx EPG in an oxygen enriched environment or near a flammable anesthetic mixture with air, oxygen or nitrous oxide. The NeuRx EPG is not categorized as AP (anesthetic-proof) or APG (anesthetic-proof category G - gas) type of equipment.

6.0 ELECTROMAGNETIC INTERFERENCE (EMI) WARNING ⚠

- **WARNING**: Some electrically powered equipment gives off electromagnetic waves which could interfere with the NeuRx EPG. When using the NeuRx EPG around electrical equipment, check the NeuRx EPG screen to make sure the EPG is working.
- **RF COMMUNICATION WARNING**: Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the NeuRx EPG stimulator, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.
- The NeuRx EPG should not be used adjacent to or stacked with other equipment and that if adjacent or stacked use is necessary, the NeuRx EPG should be observed to verify normal operation in the configuration in which it is used.

7.0 PRECAUTIONS Y

- Avoid accidental contact between connected but unused applied parts (cable or leads) and other conductive parts including those connected to ground (protective earth).
- Do NOT expose the device to excessive moisture or severe mechanical shock. If display indicates system failure, pain is felt at the electrode site, or device is exposed to moisture or shock, disconnect the cable and contact Synapse Biomedical.
- Do NOT have the stimulator connected during any type of electrical diagnostic treatment such as EMG or ECG.
- Some patients may experience skin irritation or hypersensitivity due to the electrical stimulation, the adhesive on the skin bandage, or the transparent dressing (Tegaderm™ and Op-Site™ are examples of transparent dressings) used over the gauze that covers the electrodes. Skin irritation can usually be reduced by changing the stimulus parameters or removing the adhesive.
- Patients should wear an abdominal binder when sitting in a chair as it will help their breathing.

8.0 STORAGE

- Store in a dry location within the specified temperature range.
- Store STERILE surgical components (implantable electrodes, cables, tunnelers, etc.) between 18ºC to 25ºC (64ºF to 77ºF) in an area where it is not exposed to liquids or excessive moisture. Temperatures outside the stated range can cause damage to the packaging. If stored in conditions beyond the required storage temperature, do not use the components and return to Synapse Biomedical.

9.0 PROCEDURE RISKS

- There is a risk of diaphragm penetration during the procedure, which could cause a condition known as capnothorax
- There is a risk of infection and/or inflamed tissue at the electrode implantation sites
- There is a risk of bleeding at the electrode implantation sites. Bleeding in the chest could lead to a hemothorax.
- There is a risk of nerve, tissue or organ damage as a result of the procedure
- There is a risk that the electrode wires could break off in the body leading to reduced or intermittent diaphragm pacing or failure of the pacing system
- There is a risk of cardiac arrhythmia being caused by the placement of the electrodes in the chest cavity
- There is a risk of skin irritation or hypersensitivity from the electrical stimulation or from the tape used with the electrodes or from the skin bandage that holds the electrode connections
- There is a risk that the body may not be compatible with the materials used in the electrodes and their wires
- There is a risk of choking during eating and of sleep apnea if a Passy Muir® valve is not used during the training period

- There is a risk of discomfort during the conditioning period.
- There is a risk that a patient may not have sufficient muscle reaction when using the stimulator and the product may not work for every patient
- At this time, there is insufficient clinical data to determine safety in implanting patients with cardiac pacemakers, therefore, patients should not be implanted with this device if they have a cardiac pacemaker or other implanted electrical devices.
- This product should not be used by patients with suspected or real heart problems or who have epilepsy
- The safety of this device in use during pregnancy is unknown
- The long-term effects of electrical stimulation of the diaphragm are unknown
- It is possible that stimulation from the diaphragm pacing system could stop either due to electrode breakage, cable disconnection, or stimulator failure. If one of these happens, breathing will stop. Without prompt attention, this could result in permanent disability or death. This risk is reduced by using back-up electrodes and sounding an alarm whenever the stimulator detects improper operating conditions.
- There is a risk of aspiration when using the device. While becoming used to the stimulation and timing, it is recommended that a one-way (Passy Muir®) valve on the tracheostomy be used while eating or drinking when on the pacing device. It is also recommended to use the one-way valve while sleeping to avoid upper airway obstructions. The Passy Muir® speaking valve looks like a plug with holes in it. The valve fits directly onto the end (hub) of the tracheostomy tube. It opens during inspiration to let air into the lungs and closes during exhalation to allow air to pass the vocal cords and out through the nose and/or mouth. The valve allows for more normal respiration, improves swallowing and may reduce the risk of aspiration.
- Patients may experience increased spasms with the stimulation while their body becomes used to the stimulation. This typically subsides within a few days of use.

10.0 CONTRAINDICATIONS

There are no known contraindications.

11.0 SCREENING

Candidates are patients with high level spinal cord injury resulting in dependence on mechanical ventilation. The candidate must have bilateral intact phrenic nerves below the level of the spinal cord injury. The candidate must be in otherwise generally good health. Pre-operatives tests are obtained for patients based on hospital policies/physician preference prior to general anesthesia.

12.0 DEVICE DESCRIPTION

The NeuRx DPS is a percutaneous, intramuscular, diaphragm motor point stimulation system. It is implanted using standard laparoscopic surgical techniques in an outpatient procedure. The implanted intramuscular diaphragm electrodes are connected to a four channel external stimulator at a percutaneous exit site. The stimulator provides a capacitively coupled, charge balanced, biphasic stimulation to each electrode with a

common indifferent electrode that is placed subcutaneously. The stimulator controls the charge delivered through clinician programmed parameters of pulse amplitude, pulse duration, pulse frequency, pulse ramp, inspiration time, and respiratory rate. The clinician uses a clinical station to characterize electrode response to stimulation and program the external stimulator with the patient specific parameters. The user connects the stimulator and turns it on for use; no other controls are available or necessary for operation.

12.1 Implantable Components

STERILE EO

Surgical components are provided double-pouch packaged in medical grade Dupont™ Tyvek® pouches and EO sterilized

12.1.1 PermaLoc® Intramuscular Electrode

The stimulation is delivered to the phrenic nerve motor point through four intramuscular electrodes implanted into the diaphragm. Two electrodes are placed into each hemi-diaphragm at locations, found during surgical mapping, that elicit the greatest contraction of the diaphragm. This may be obtained by a single motor point, where the main trunk of the phrenic nerve enters the diaphragm, to produce a diffuse contraction or at two individual branches that recruit the anterior and posterior portions of the diaphragm. The electrodes are tunneled directly to the percutaneous exit site on the chest.

The intramuscular electrode is a double helix wound lead with exposed 316LVM stainless steel stimulating surface and polypropylene reinforced core and barb. The body of the lead is insulated with PFA (perfluoroalkoxy) fluoropolymer coating and terminated in a 316L stainless steel pin with a silicon reinforcing sleeve. All of the materials have a history of long-term implantable use as part of previously approved products. The lead is 61cm in overall length, 0.75mm in diameter, and has a 9mm de-insulated stimulating tip.

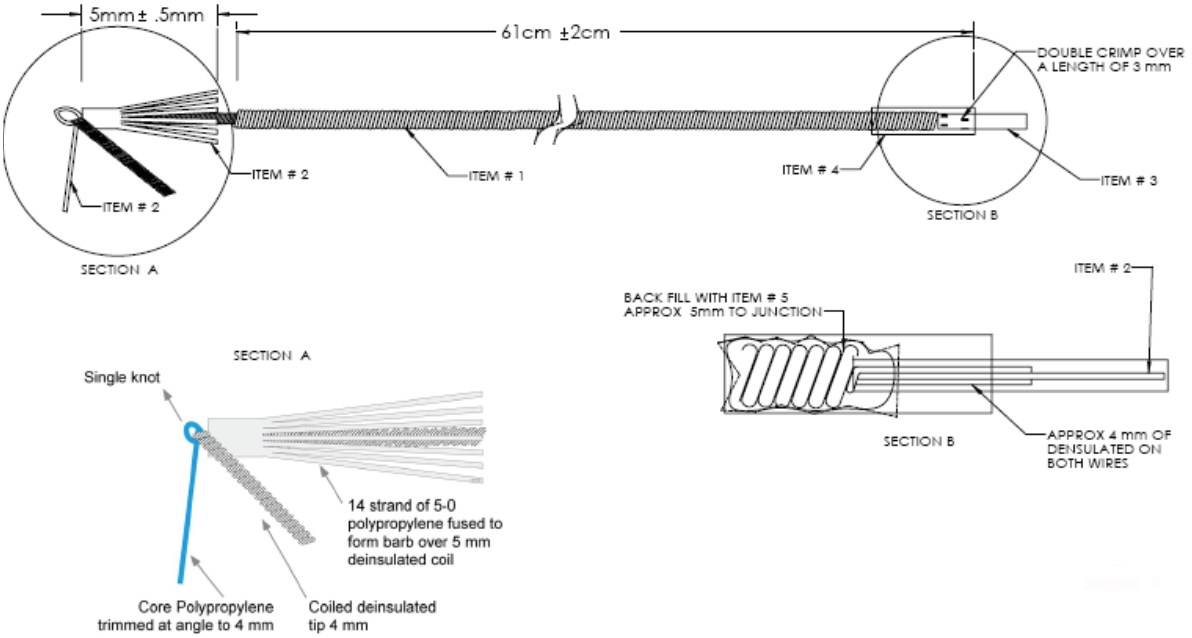


Figure 1. PermaLoc® Electrode

12.1.2 Indifferent Electrode (Anode)

The indifferent electrode provides a common return current path for all of the electrodes implanted in the diaphragm. It is implanted in the subcutaneous tissue of the lateral chest region and is tunneled to the percutaneous exit site. The lead is fabricated of the same double helix wound 316LVM stainless steel as the intramuscular electrode and percutaneous extension lead. It is also terminated in a 316L stainless steel pin at one end and 7cm de-insulated for the return electrode tip. The overall length is approximately 19cm with a 0.75mm diameter.

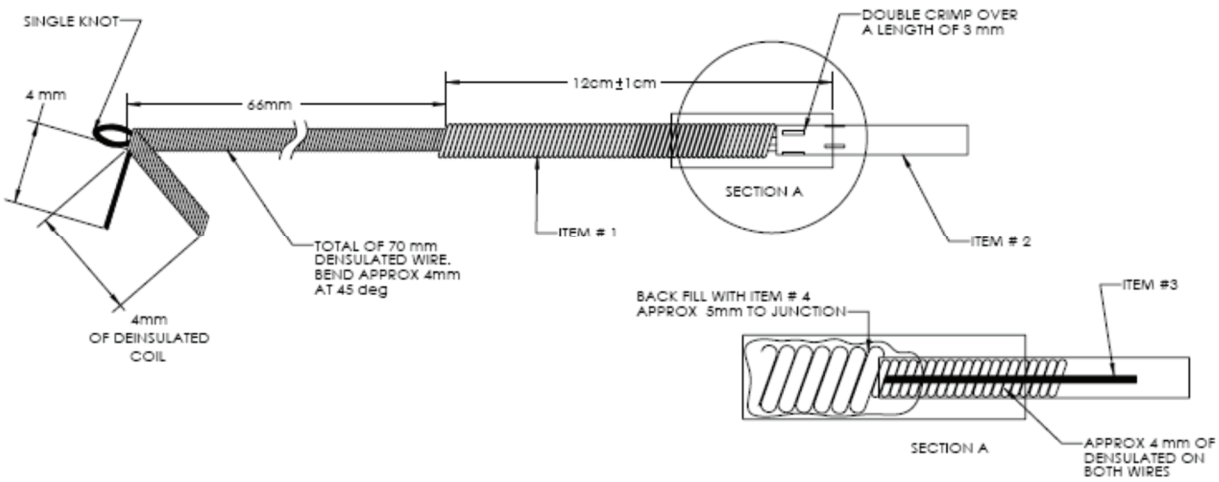


Figure 2: Indifferent Electrode

12.2 External Components

12.2.1 NeuRx DPS External Pulse Generator (EPG)

The patient external pulse generator (EPG) an external four channel, battery powered device that controls the stimulus output and respiratory timing. The four output channels are independently controlled, capacitively-coupled, biphasic outputs with a common return. The device is packaged in an impact resistant plastic enclosure with patient cable connector on the top, display and power buttons on the front and replaceable battery compartment on the back. A programming connector is located in the battery compartment for connection to the clinical station.

The device is powered from a user replaceable primary 1.5 volt alkaline battery and a secondary 4.0v rechargeable battery. The internal secondary battery recharges from the primary battery upon replacement. This configuration allows a charged backup battery in the unit at all times to allow sufficient time for the user to replace the primary battery. The display will indicate when the device is operating from the internal backup battery and provide an audio indicator when the internal backup battery reaches low charge remaining. Additional indicators are given for impedance of each channel on the display and an audio indicator in the event of an impedance too high for the constant current supply.

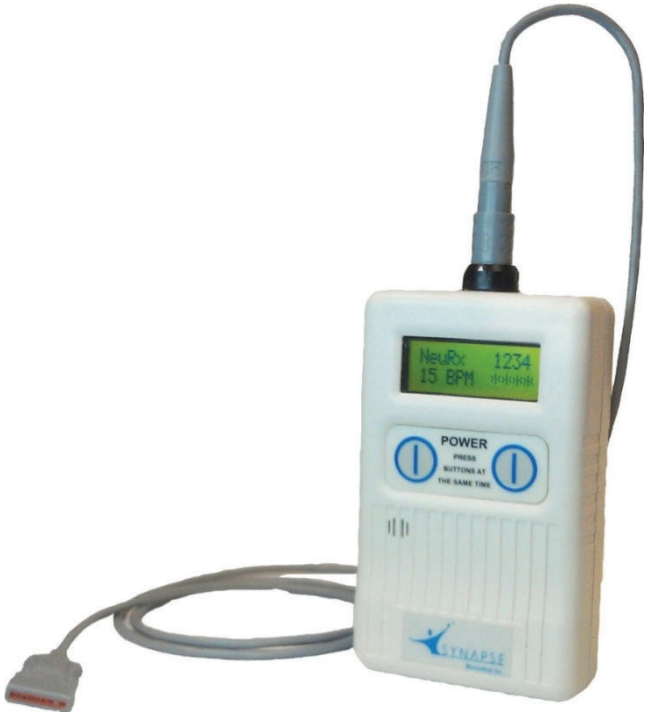


Figure 3. NeuRx DPS External Stimulator

The next figure shows an actual pulse output of a 20mA by 100usec stimulus pulse through a nominal load impedance of 1.0KΩ. The measured waveform has a -20v cathodic pulse followed by the load-regulated charge-balancing anodic phase.

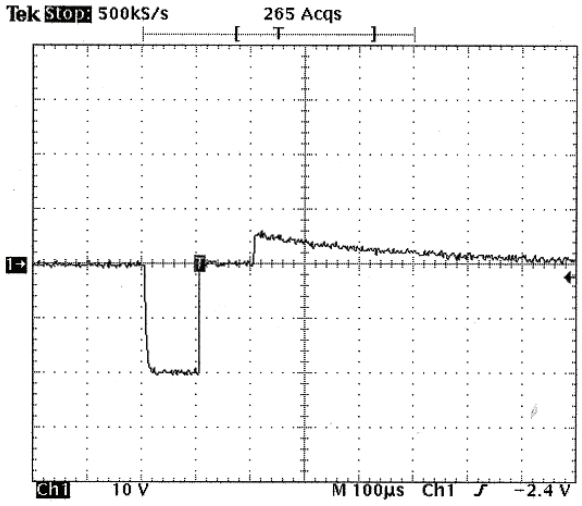


Figure 3: Pulse output of stimulus pulse through nominal load impedance

The next figure shows the timing relationship between stimulus outputs 1 and 2 to demonstrate the timing relationship between successive stimulus outputs. There is a

fixed 4msec time skew between successive stimulus outputs channels. Stimulus outputs 3 and 4 would then follow after output 2 with the same time skew.

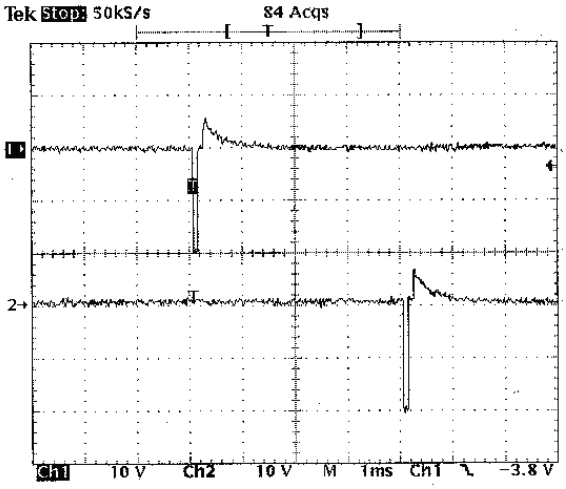


Figure 4: Timing relationship between successive stimulus outputs

12.2.2 Patient Cable

A five conductor cable is provided that connects from the external pulse generator to the electrode connector socket. The pulse generator end of the cable is a positive locking medical grade plastic shell connector. The cable is a silicone jacketed, multi-conductor, shielded cable that is 0.75m in length. The electrode connector end is a custom molded five conductor connector. It is a precision mated strip of pins embedded in the molded PVC. The cable assembly has passed biocompatibility testing.

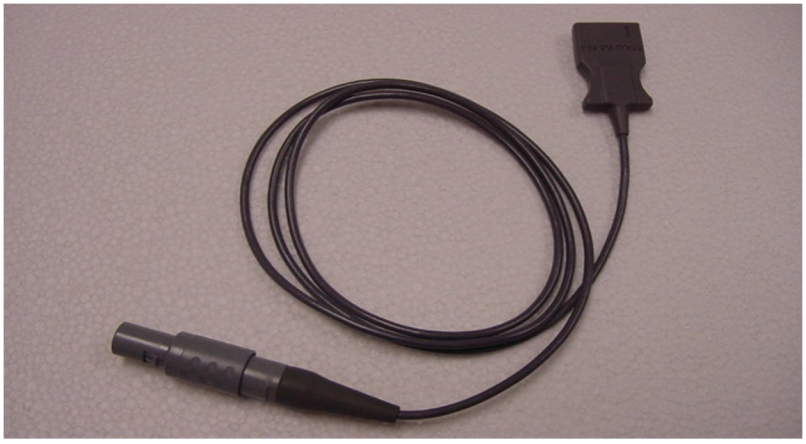


Figure 5: Patient Cable

12.2.3 Connector Holder

A disposable holder secures the electrode connector socket on the chest. A custom molded clip is secured to a 7.5 x 2.5cm spunlace tape. The spunlace tape is MED5322 hypoallergenic fabric medical tape intended for applications to the skin for sustained periods.

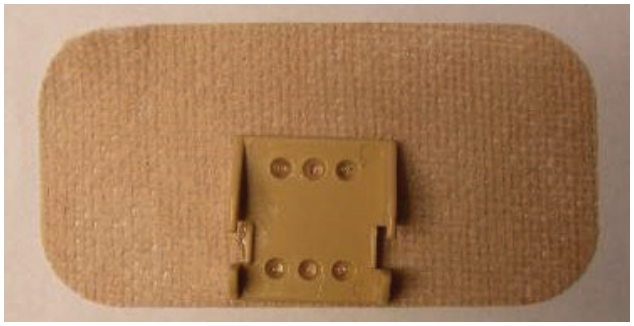


Figure 6: Connector Holder

12.2.4 Electrode Connector Socket Kit

Each electrode is terminated into a precision ITT Canon socket. The individual sockets are crimped onto the electrode and inserted into a carrier strip. The sockets are inserted into the carrier strip in a set sequence to mate with the patient cable. The crimp connections are protected with a strain-relief boot.

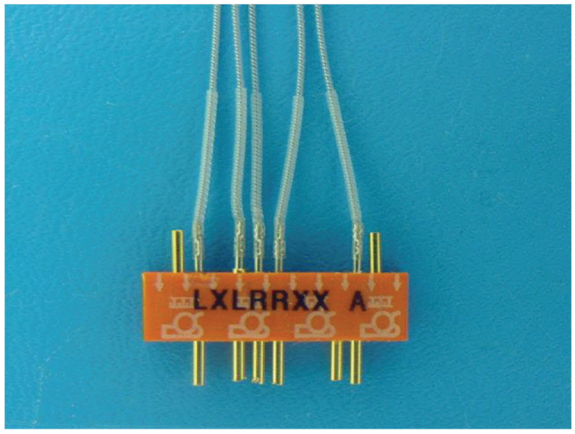


Figure 7: Electrode Connector Block

12.2.5 Strain-Relief Boot

A flexible boot is attached to the electrode connector block and then filled with silicone. The boot acts as a mold creating a strain-relief for the electrode leads as they exit the electrode connector block.

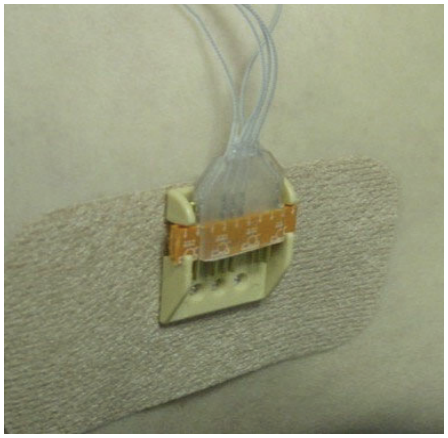


Figure 8: Molded Strain-Relief Boot

12.2.6 Backup Indifferent Electrode Interconnect

A interconnect assembly is provided that allows the temporary connection of a surface indifferent electrode. With redundancy in all other components, this assembly provides redundancy for the implanted anode. In case of a malfunction with the implanted anode, breakage or extraction, this component can be used to replace that function and thereby allow continued therapy without need for immediate re-insertion of an implanted anode. The availability of a backup indifferent electrode minimizes the interruption of stimulation.

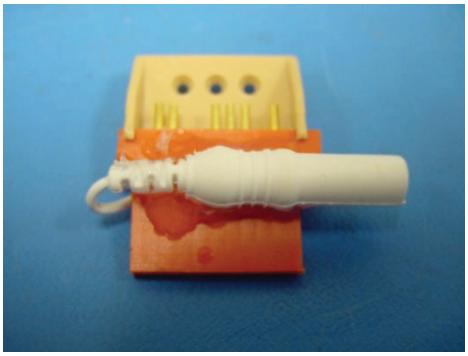
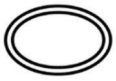


Figure 9: Backup Indifferent Electrode Interconnect

12.3 Surgical Components



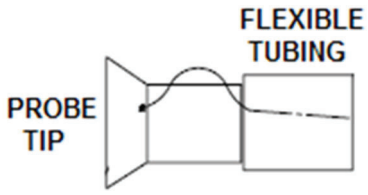
With the exception of the Solid State Pressure Transducer, Surface Anode, Clinical Station and Disposable Electrode Delivery Tool, all surgical components are provided double-pouch packaged in medical grade Dupont™ Tyvek® pouches and EO sterilized.

The Electrode Delivery Instrument is steam-sterilized at the surgical site.

The Disposable Electrode Delivery Tool is irradiation sterilized in a sealed single sterile barrier package.

12.3.1 Mapping Instrument

The initial step in the surgical implementation is the laparoscopic mapping of the diaphragm. This may be performed by introducing a specialized 5 mm mapping instrument to stimulate the inferior surface of the diaphragm in a grid pattern to identify optimal implantation sites of the intramuscular electrodes. The mapping probe is applied to sequential sites on the diaphragm by the surgeon and secured by applying the operating room vacuum through the central lumen of the probe. Stimulation is applied in either a twitch or burst mode from the clinical station to elicit an abdominal pressure change.



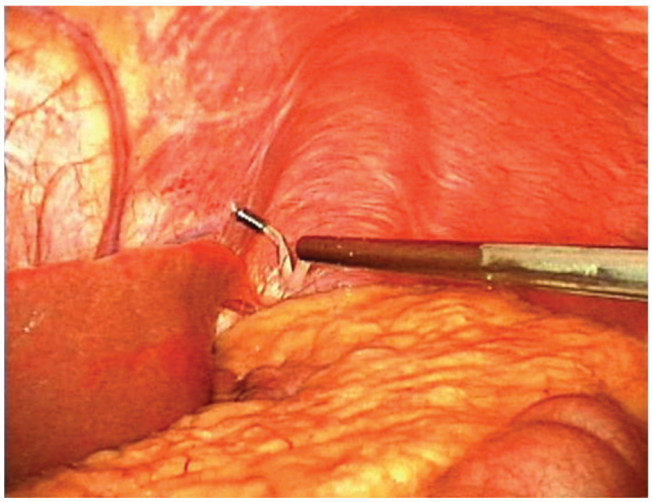


Figure 10: Mapping Instrument

12.3.2 Transducer to Trocar Pressure Tube

A one meter section of PVC tubing, with male luer lock connectors on either end, is used to connect a Trocar port to the solid state pressure sensor.

12.3.3 Solid State Pressure Sensor

A differential, 1 PSI full scale, pressure sensor transduces the abdominal pressure changes to an electrical signal for the clinical station. It connects to the pressure tube with a female luer lock and to the clinical station with a positive locking medical grade connector. The electrical signal provides an indication of relative pressure change.

12.3.4 Cable Set

A set of cables with touch-proof connectors are used to connect off the sterile field from the mapping instrument to the clinical station. A set of 3m meter cables connect to the mapping instrument or clip leads to test implanted electrodes. Another cable connects from the surface anode to the clinical station.

12.3.5 Surface Anode

A standard 2" x 3.5" electrotherapy surface electrode is used during intra-operative mapping.

12.3.6 Disposable Electrode Delivery Tool

A 10mm disposable laparoscopic instrument is used for implantation of the electrodes in the diaphragm. The barbed intramuscular electrode is loaded in the lumen of the instrument with the de-insulated barb extending out of the needle. The skirt of the polypropylene barb is loaded inside of the needle. When the needle is extended and inserted between the muscle fibers, parallel to the diaphragm surface, the de-insulated barb catches on the fibers and the lead is drawn out of the lumen as the instrument is withdrawn.

Figure 11: Disposable Electrode Delivery Tool

12.3.7 Tunnelers

A set of 304 stainless steel 12 gauge cannulae are used to tunnel implanted leads to the percutaneous exit site.

12.3.8 Clinical Station

There are three primary aspects of the device implementation that the clinical station provides. The station provides intra-operative mapping functionality, incorporates NeuRx DPS External Pulse Generator functionality, and NeuRx DPS External Pulse Generator programming capability.

The Clinical Station provides intra-operative stimulation and sensing of stimulated response. This surgical mapping mode utilizes the surgical components listed above to provide twitch or burst stimulation to record and display the abdominal pressure response through the solid state pressure sensor. A pulse generator mode is used to test the channels individually and in combination at the end of the surgery to make sure that all electrodes are intact and providing the anticipated response.

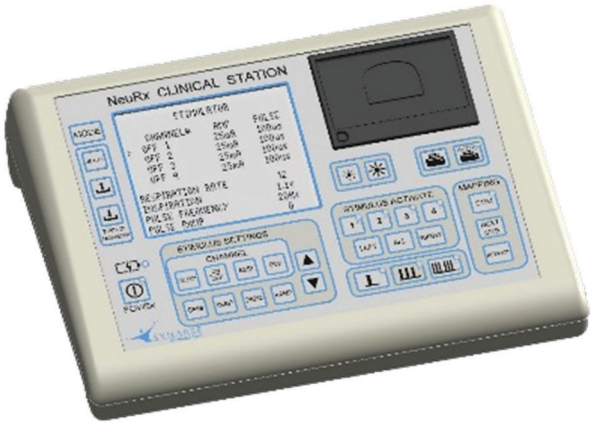


Figure 12: Clinical Station

13.0 Principles of Operation

The NeuRx DPS is a percutaneous, motor point, stimulation device that is implanted in the diaphragm during an outpatient laparoscopic procedure. The following procedural explanation of the method of use links the design and performance specifications of the device components to specific steps which enable the NeuRx DPS System to achieve its intended use:

1. *The locations for implantation are identified by electrically mapping the inferior aspect of the diaphragm.*

   The Mapping Probe is an optional 5mm instrument which was designed to stimulate the inferior surface of the diaphragm. The design includes a flared probe tip to provide more contact surface to aid in suction and electrode retention.

   The Cable Set includes 3 sets of cables designed for specific functions:
   a. A set of 3m cables connect to the mapping instrument or clip leads to test implanted electrodes.
   b. Another cable connects from the standard 2” x 3.5” electrotherapy surface electrode (i.e., Surface Anode) to the Clinical Station.
   c. Set of cables equipped with touch-proof connectors, which are used to connect off the sterile field from the Mapping Probe to the Clinical Station.

   During the mapping process, the Clinical Station operates in surgical mode and delivers twitch or burst stimulation to elicit an abdominal pressure change.

   The Solid State Pressure Sensor is equipped with a female luer lock which enables it connect to the Transducer to Trocar Pressure Tube. The Pressure Sensor also has a positive locking medical grade connector to connect to the Clinical Station. The Pressure Sensor is a differential, 1 PSI full scale, pressure sensor which transduces the abdominal pressure changes to an electrical signal for the Clinical Station.

The surgeon applies the Mapping Probe to sequential sites on the diaphragm (in a grid pattern) and uses the abdominal pressure change readings to identify optimal implantation sites of the intramuscular, PermaLoc® Electrodes.

Alternatively, a laparoscopic dissector can be connected to the clinical station for mapping.

2. *Intramuscular electrodes are surgically implanted in the diaphragm muscle in proximity to branches of the phrenic nerve without making contact or manipulating the nerve.*

   The Electrode Delivery Instrument is used to implant the intramuscular (PermaLoc) electrodes. Its unique laparoscopic design includes a needle extension feature which enables electrodes to be loaded and implanted on the muscle fibers of the diaphragm.

   PermaLoc Electrodes are designed to be between 59cm to 63cm and are equipped with electrical pin connectors to simplify the surgical procedure and prevent disconnection.

   The stimulator mode on the Clinical Station is used to test the channels individually and in combination at the end of the surgery to make sure that all electrodes are intact and providing the anticipated response. The amplitude, pulse width, frequency, and pulse ramping response are each characterized to optimize the tidal volume and patient comfort on a per breath basis.

3. *The electrode leads are tunneled, subcutaneously, to a percutaneous exit site on the lateral chest region.*

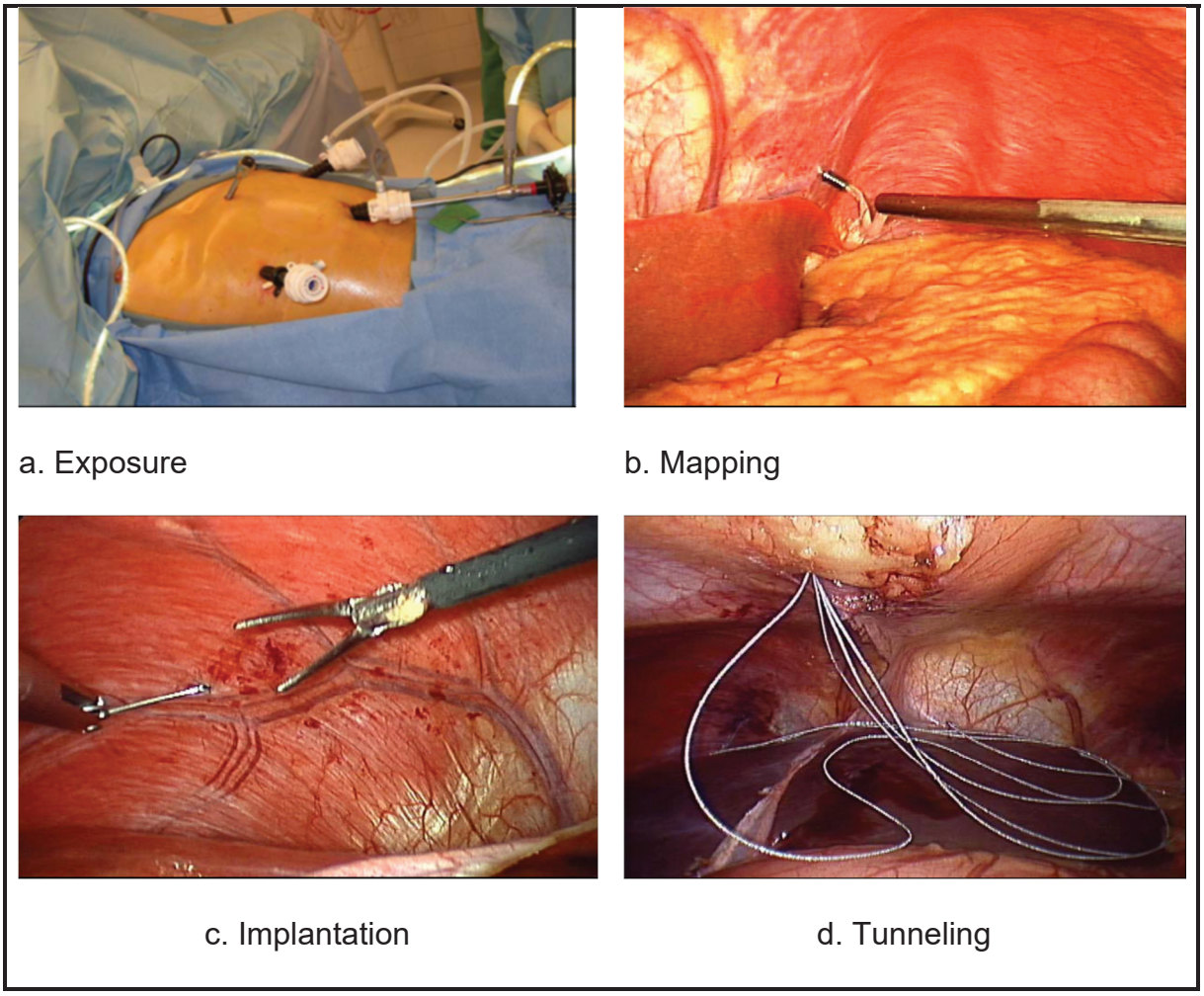
   Lead Tunneler Set, which is a set of 304 stainless steel 12 gauge cannula, is used to tunnel implanted leads to the percutaneous exit site.

4. *An indifferent return electrode (anode) is placed subcutaneously and exits at the same chest location.*

   The design of the Indifferent Electrode allows it to provide a common return current path for all of the electrodes implanted in the diaphragm. The lead is fabricated of double helix wound 316LVM stainless steel and one end is terminated in a 316L stainless steel pin. The other end is a 7cm de-insulated, return electrode tip.

5. *These electrodes are connected to an external stimulator that controls the timing and level of diaphragm pacing stimulation. Each electrode may be controlled individually in terms of charge (pulse duration and pulse amplitude) delivered and grouped together to recruit the diaphragm muscle to elicit the desired level of inspiratory effort.*

The NeuRx EPG provides four outputs sharing a common anode return electrode. To prevent direct current output leakage each cathodic stimulus output is capacitively coupled by redundant capacitors that are in series with each output contact. Each output delivers a current waveform providing zero net-charge imbalances over time.



a. Exposure

b. Mapping

c. Implantation

d. Tunneling

Figure 14. Surgical Electrode Implantation

6. *The stimulation levels and timing are programmed for the specific patient needs by a clinician and are not adjustable by the device user.*

   The Clinical Station is also equipped with External Pulse Generator programming capability. The following parameters are adjustable by using the programmer:

Parameter Description	Range	Resolution
ENABLE: Output Enable	Outputs 1 to 4	n/a
I_C: Cathodic Current Amplitude	5 to 25 mA	1 mA
PW: Cathodic Current Pulsewidth	20 to 200 usec	10 usec

Parameter Description	Range	Resolution
PER: Output Pulse Period	50 to 200 msec	1 msec
BPM: Respiratory Rate	8 to 18	1
INSP: Inspiration Time	0.8 to 1.5 sec	0.1 sec
P_{MOD}: Pulse Modulation Count (First Pulsewidth = 20% PW)	0 to 10	1

Figure 15. Stimulation Parameters

The parameters listed below are programmable on a global output basis:

- PER - Output Pulse Period
- BPM – Respiratory rate
- INSP - Inspiration Time
- P_{MOD} - Pulse Width Modulation Count

The following parameters are programmable on an individual output basis:

- I_C - Cathodic Current Amplitude
- PW - Cathodic Current Pulsewidth
- ENABLE - Output Enable Control

14.0 PATIENT INFORMATION

See the document “Synapse Biomedical NeuRx® Diaphragm Pacing System Patient Information” (PN 77-0090) provided with the device. This document is meant to be provided to the patient.

15.0 PREPARATION FOR PROCEDURE

15.1 Verifying NeuRx® Clinical Station Charge:

The NeuRx® Clinical Station should be charged the night before a planned surgery to ensure sufficient charge for the case. To check the charge of the NeuRx Clinical Station, simultaneously press the POWER button and the LINE FEED button. Release the POWER button and after the “Synapse Biomedical” screen appears release the LINE FEED button. A printer system check and battery charge indication will be printed. *[Note: a minimum of 4 stars is required to accomplish the surgical procedure.]* Turn the NeuRx® Clinical Station off until needed. Do not use the NeuRx® Clinical Station while it is plugged into wall power.

16.0 OPERATING ROOM PREPARATION/ASSEMBELY

Prior to beginning procedure and patient's arrival to the operating room, verify the sterile seal on all of the Disposable Electrode Delivery Tools have not been compromised.

The Sterile Surgical Kit is packaged in the order of use during the case. The circulating staff should remove the following items from the kit and introduce onto the sterile table:
Trocar Tubing
Mapping Probe
Blue Cable Set
4 Permaloc® Electrodes

16.1 Preparation of the Disposable Electrode Delivery Tools:

The scrub staff should preload one Permaloc® Electrode into one of the Disposable Electrode Delivery Tools. The other Disposable Electrode Delivery Tool should not be loaded as the surgeon may want to use it to orient the entry angle of the instrument into the diaphragm.

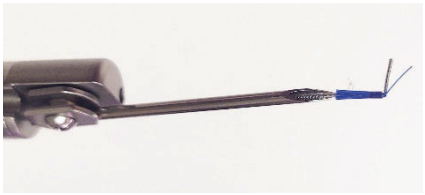
A bowl of sterile water or saline may be used to lubricate the electrodes prior to inserting into the Disposable Electrode Delivery Tool. Use a syringe filled with saline to lubricate the Disposable Electrode Delivery Tool to aid in electrode insertion. The Disposable Electrode Delivery Tool can be loaded with the needle locked at 90˚ or 180˚.

- Option #1: Loading electrode with needle at 180˚:
  - Squeeze handle to the second locking position and lock the needle position by pushing the slide button.
  - Lay silver pin end of electrode into needle tip bevel area.
  - Keep electrode parallel to needle to not damage silicone sheath on electrode while loading through the tube of the tool.
  - DO NOT damage electrode by forcing through the needle bevel.
  - Continue to push electrode through the needle until the tip of the electrode nears the bevel of the needle.

- Place thumb against bevel of the needle point and pull the remaining electrode through the tube of the tool. Ensure the blue tip is completely in the bevel of the needle.

- Verify that only the electrode stimulating tip of the electrode is exiting the needle tip of the Disposable Electrode Delivery Tool.
- While holding handle, unlock the needle position by pushing the slide button.

- Option #2: Loading electrode with needle at 90°:
  - Squeeze handle to the first locking position and lock the needle by pushing the slide button.
  - Lay silver pin end of electrode into needle tip bevel area (1)
  - Keep electrode parallel to needle to not damage silicone sheath on electrode.
  - DO NOT damage electrode by forcing through the needle bevel.
  - Push electrode through the needle until the tip of the electrode nears the bevel tip.



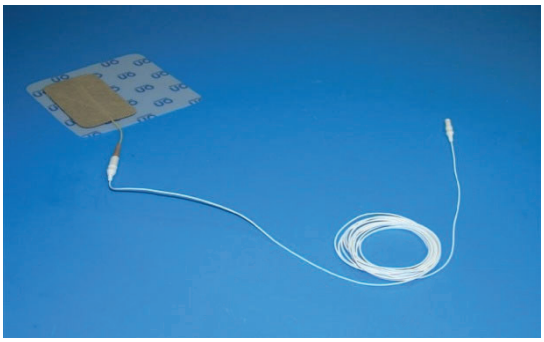
  - Insert silver pin end of the electrode into the electrode tube opening (2)
  - Continue to push electrode through the electrode tube until exits tool.
  - Place thumb against bevel of the needle point and pull the remaining electrode through the tube of the tool. Ensure the blue tip is completely in the bevel of the needle.

  - Verify that only the electrode stimulating tip of the electrode is exiting the needle tip of the Disposable Electrode Delivery Tool.
  - Unlock the needle position by pushing the slide button.

Repeat this procedure for loading electrodes into other Electrode Delivery Instruments.

17.0 Patient Preparation

Ask the circulating nurse to remove the white Touch Proof Extension Lead and packet of Surface Electrodes from the Sterile Surgical Kit. Open packet of surface electrodes and remove one sheet from packet. Attach the white Touch Proof Extension Lead to one of the surface electrodes.



Surface Electrode with Touch Proof Extension Lead

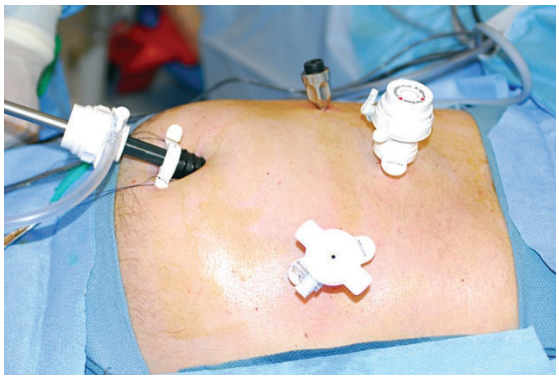
Once the patient is placed on the table and prior to sterile draping, ask staff to place the surface electrode on to the patient's thigh. Extend the White Touch Proof Extension Lead away from the sterile field so you have access to it when needed for mapping the diaphragm.

Place the NeuRx® Clinical Station on small surgical table that can be easily moved into position once procedure starts. It is recommended you can see the monitor to visualize diaphragm contraction. Do not make any connections to the NeuRx® Clinical Station until the surgeon is ready to begin mapping.

18.0 Surgical Procedure

18.1 Establishing Laparoscopic Ports

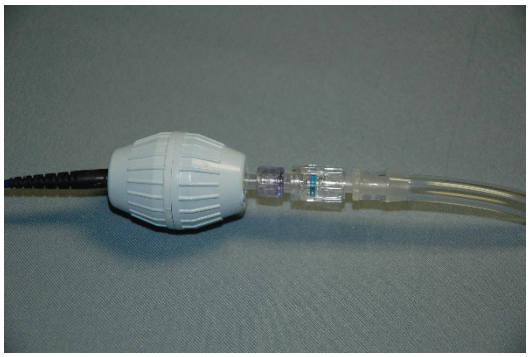
The operation is done in the supine position with no neuromuscular blocking agents. The patient's abdomen and chest is prepped and draped in the usual sterile fashion. Four ports will need to be inserted into the abdominal cavity: one for optics, two lateral working ports for the mapping probe and one epigastric port for electrode insertion instruments and the exit site from the abdominal cavity for the electrode lead wires. During this phase, any abdominal adhesions are released and gastrostomy tube tracts are removed if they are in the way of implantation of the diaphragm pacing system. The falciform ligament is divided which allows easier visualization of the medial aspect of the right diaphragm and provides an easier exit of the pacing electrodes through the epigastric port. Standard laparoscopic principles are followed with a typical setup.



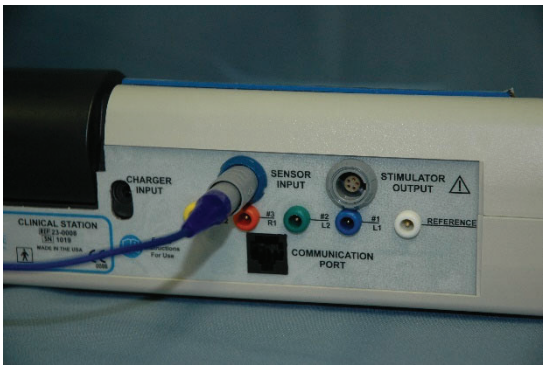
4 ports insertion

18.2 Mapping the Diaphragm:

First, the Falciform Ligament is cut to allow better exposure and then the electronic scalpel/cauterizing instrument is removed. Proceed by connecting the trocar tubing to the lateral trocar closest to where the NeuRx® Clinical Station is set up. Both ends of the tubing are the same. One end of the Trocar Tubing should be attached to the trocar and the other end should be passed off the sterile field. Secure the Active Sensor Module (pressure transducer) to the end of the Trocar Tubing that was passed off by twisting the luer lock connection to the transducer port.



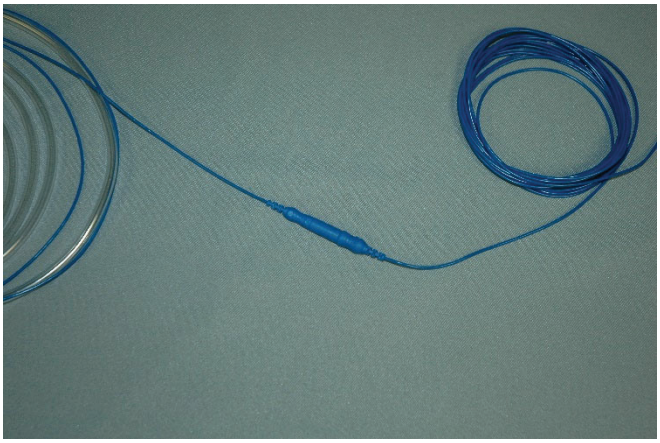
Connect the cable from the pressure transducer to the blue “SENSOR INPUT” port on the back of the NeuRx® Clinical Station.



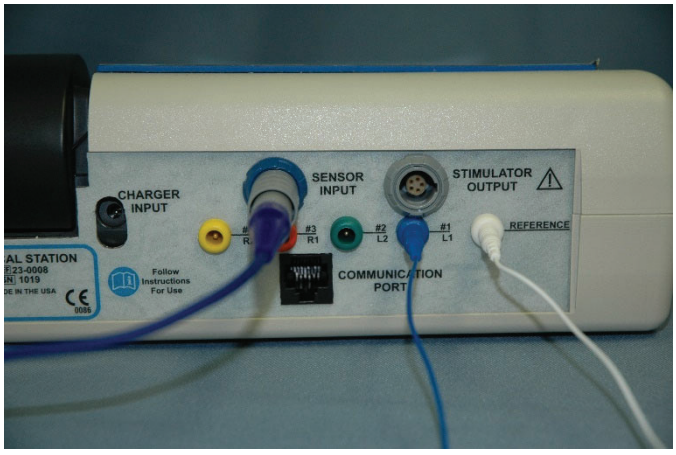
The transducer allows the NeuRx® Clinical Station to measure the change in abdominal pressure when the muscle contracts and is not a direct reflection of muscle strength. A larger number correlates to a greater diaphragm contraction and the quality of muscle contraction is also visualized. A larger number with a large part of posterior diaphragm contracting is optimal.

Insert the white Touch Proof Extension Lead into the white port on the back of the NeuRx® Clinical Station labeled “REFERENCE”.

Assembly of the Mapping Probe and Blue Touch Proof Cable set will occur on the sterile field and be done by the surgical team. Connect the appropriate end of the blue touch proof cable set to the end of the blue cable on the mapping probe.



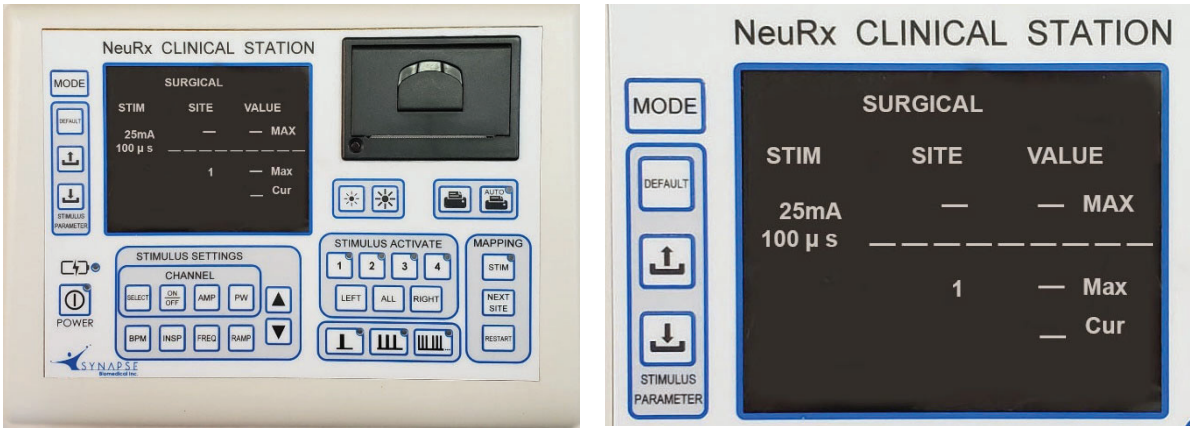
The other end of the blue cable should be passed off of the sterile field and attached to the blue port labeled “#1/L1”on the back of the NeuRx® Clinical Station.



Set the blue alligator clamp aside on the sterile field. This will be used to check each electrode after implantation. Move the white clamp on the suction tubing of the mapping probe closer to the mapping probe while keeping it on sterile field. Keep clamp in locked position when not in use. Standard suction tubing is then attached to the mapping probe.

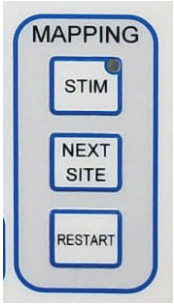
19.0 Using the NeuRx® Clinical Station for Mapping the Diaphragm

Turn on the NeuRx® Clinical Station by depressing the power button. The NeuRx Clinical Station will be in “stimulator” mode. Press the “mode” button on the NeuRx Clinical Station and scroll to the “SURGICAL” function.



Locate the “Enable Auto Print” button under the printer. This feature will allow you to have a documented record of diaphragm mapping. Press the “Enable Auto Print” button to record the diaphragm mapping. Record the date, patient name and location you are mapping (Right or Left).

When the surgeon places the mapping probe on to the diaphragm, they will request a “stim”. Locate the “STIM” button in the “MAPPING” section of the NeuRx® Clinical Station. To “stim”, press the “STIM” button and tell the surgeon the number that appears on the screen. This number represents that change in abdominal pressure. Press the “next site” button to record that number and clear the screen for the next mapping point.



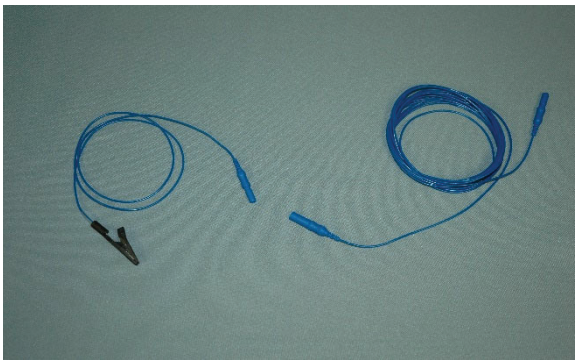
The primary electrode implant site is identified at the location of maximal pressure change in each hemi-diaphragm and visualization of diaphragm muscle contraction. A secondary electrode site is identified as either a backup to the primary site or at a location in each hemi-diaphragm that recruits another phrenic nerve motor point region [e.g. anterior or posterior] of the diaphragm at a similar magnitude. The two locations on each hemi-diaphragm are then marked using a marker. The process is repeated for the opposite hemi-diaphragm.

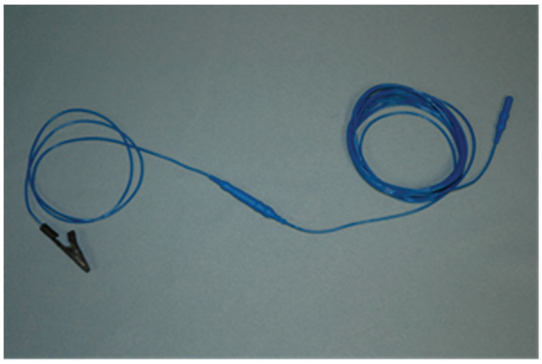
At times, there may be very low readings of a change in abdominal pressure or very little diaphragm may move. This occurs in patients with an extremely de-conditioned diaphragm or if the diaphragm has more lower neuron involvement than the pre-operative tests indicated. To confirm that this is not a technical problem, proceed with the following:

In conditions of LOW READING use steps 1-7 below;

1. Confirm that all connections are secure.
2. Confirm that port the trocar tubing is attached to is open.
3. Look for electrical artifact on the anesthesia cardiac rhythm monitor to verify stimulation.
4. Confirm that no paralyzing agent was given by the anesthesiology team and, if so, confirm that it was reversed.
5. Decrease insufflation pressure which decreases the force the diaphragm will have to contract against and may allow better visualization of diaphragm movement.
6. Allow diaphragm to rest; the repeated stimulation of a deconditioned muscle will lead to fatigue
7. Use “train” if “stim” cannot be measured or visualized.
    a. The use of “train” to map the diaphragm will quickly fatigue the muscle.
    b. To initiate a Train, depress the Pulse train button followed by the STIM button. [A Train pulse is a stimulation lasting 1.1 seconds in duration]

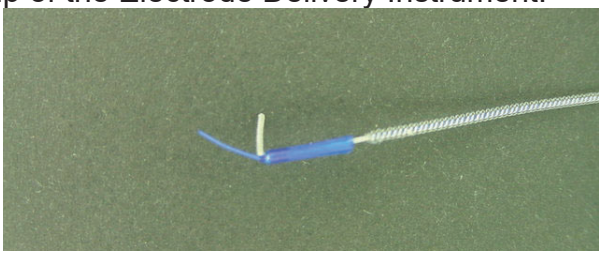
Upon completion of mapping the four electrode sites, disassemble the mapping probe from the blue extension cable. Place the mapping probe on the sterile back table. Assemble the sterile blue alligator clamp to the blue extension cable. Secure the blue alligator clamp to the sterile field with hemostat or by clamping to the sterile drape.





20.0 Implantation

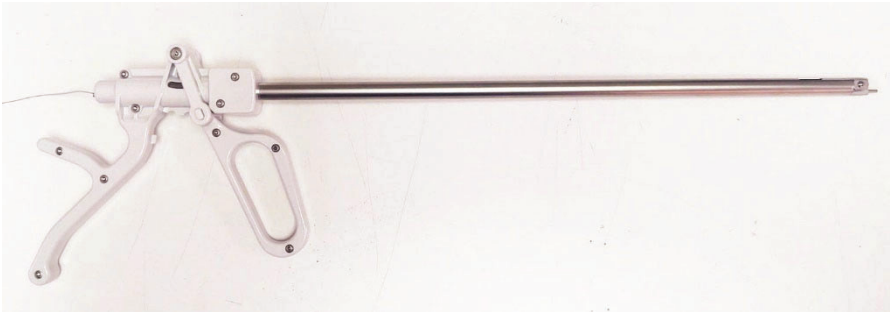
Once the primary and secondary electrode sites are identified in each hemi-diaphragm, the implantation phase begins. Placement begins with the posterior electrodes. Verify that only metal filament [*appears white due to material properties*] of the IM electrode is exiting the needle tip of the Electrode Delivery Instrument.



IM Electrode with skirt

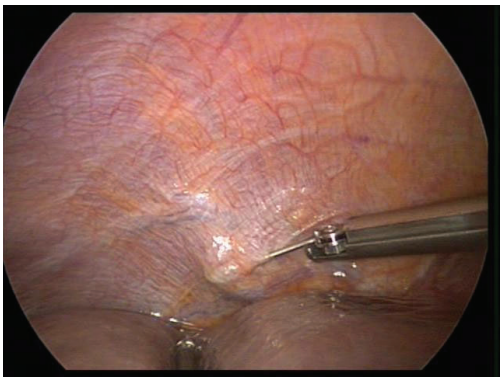
[*Ensure that the 5mm blue skirt is inside the needle bevel for easier introduction into the diaphragm. The blue skirt secures the IM electrode into the diaphragm muscle*]. Using the handle, position the needle tip retrograde along the barrel of the instrument and introduce the instrument in the abdomen through the 12mm port.

[*Note that the instrument's needle extends through a circular motion and requires 1.35" arc of free space to transverse and open*.]

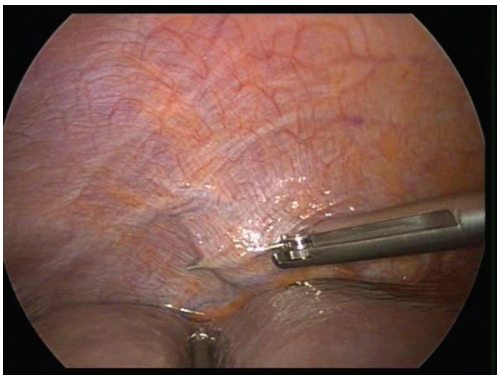


Surgical Disposable Electrode Delivery Tool

Using the handle of the instrument carefully extend the needle. Slowly advance the tip of the needle at an angle parallel to the plane of the diaphragm that results in entry into the superficial layer of the hemi-diaphragm. [*Since the diaphragm is typically 3mm - 4mm thick, particular attention needs to be placed on the angle to avoid entry into the thoracic cavity]*.

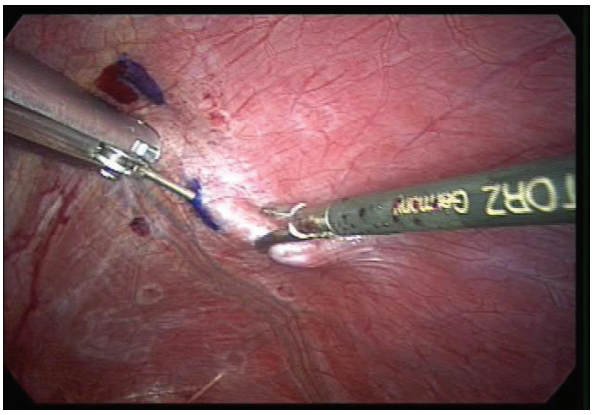


Electrode Insertion



Electrode Insertion

Externalization of the needle tip in the abdominal cavity would confirm superficial plane of entry into the diaphragm. The laparoscopic dissector may be used to assist in the positioning of the electrode at the desired site on the diaphragm. The dissector should be used to gently grasp the diaphragmatic tissue surrounding the needle to provide counter traction as the needle is retracted from the diaphragm.



Counter Traction on IM Electrode

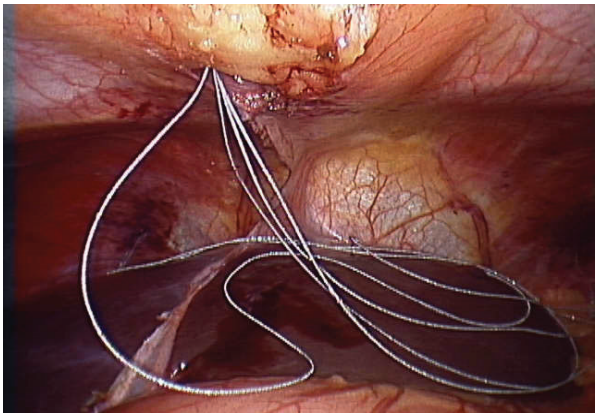
Using the dissector, grasp the base of the electrode exiting the diaphragm and gently pull about 5-7cm of the electrode from the instrument. Do not pull the electrode from the diaphragm. The needle of the instrument should be extended while the instrument is withdrawn from the abdomen through the trocar. Hold the electrode while the instrument is withdrawn from the trocar to ensure the electrode is not pulled out of the diaphragm. When the Disposable Electrode Delivery Tool is through the trocar, the electrode will be at the tip of the needle. Gently grasp the electrode with your fingers and completely remove it from the instrument. Hand the Disposable Electrode Delivery Tool to the scrub staff to be reloaded in preparation for the next side.

The silver end of the electrode will be out of the trocar. Take the blue alligator clamp and connect it to the silver electrode tail. The NeuRx® Clinical Station operator will run a STIM test to verify muscle twitch and a Train test to verify full muscle contraction. If the response is an X [*open circuit or unacceptable resistance*], reposition the alligator clamp ensuring that alligator clamp is making good contact with the silver pin [*avoiding the silicon sleeve*] and retest. If the response is still “X”, then use a 5mm dissector to manipulate the electrode and retest again. If the response continues to be an X, the

electrode may need to be removed and a new electrode may need to be introduced into the diaphragm.

The second IM electrode is inserted in a similar fashion and tested to confirm appropriate contraction of the hemi-diaphragm. The procedure is repeated now on the opposite hemi-diaphragm.

After all electrodes are implanted, all 4 leads are carefully brought out through the epigastric trocar, separated and marked with steri-strips® noting the right and left side. The epigastric trocar is then removed.

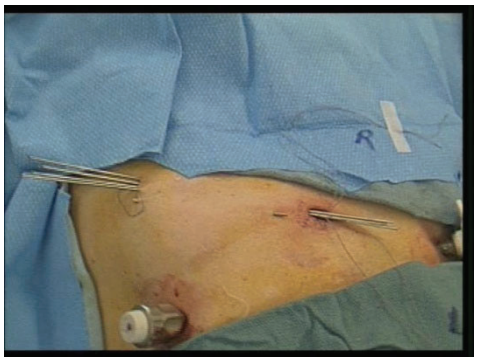


IM Electrodes Exit

21.0 Routing

Use a local anesthetic around epigastric port entrance site and the marked exit sites before tunneling. Four tunnelers are passed subcutaneously to an acceptable location on the patient's chest or abdomen in a vertical line. An additional indifferent electrode is placed subcutaneously in the most inferior or caudad location with a separate tunneler and percutaneous exit site.

The tunnelers are then flushed to enable the electrodes to pass through the lumen. In a standard fashion, the two left electrodes are fed down the two cephalad tunnelers and then the two right electrodes in the more caudad tunnelers.



Tunneling IM electrodes

The steri-strips® are removed, the IM electrodes are fed down the tunnelers cannula and the exit sites are marked [L, L, R, R, A].

At this time, the abdomen is once again insufflated and the excess leads are retracted into the abdomen and placed immediately over the liver, away from any of the bowel. The leads need to be approximately 1-2 cm exiting the chest and a final system check will be conducted.

22.0 Final Check of Electrodes

The NeuRx® Clinical Station now needs to be in the "STIMULATOR" mode and placed to maximal stimulus settings (increase Pulse Width to 200us) to check for cardiac interaction. To do this, press the "MODE" until the "STIMULATOR" mode is indicated on the screen.

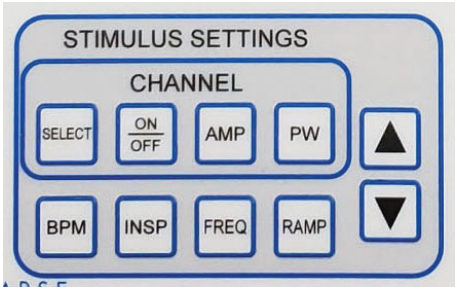
22.1 Changing Setting on the NeuRx® Clinical Station for Final Intraoperative Check:

Place the NeuRx® Clinical Station in "STIMULATOR" mode by using the "MODE" button. Note that the NeuRx® Clinical Station will default to this mode and the selector will be on Channel 1 when it is turned on.

The NeuRx® Clinical Station will display default setting of AMP = 25mA, Pulse Width = 100µs, Respiration = 12 BPM, Inspiration Time = 1.1 seconds, Frequency = 20Hz, Pulse Ramp = 0.

22.1.1 Adjusting Pulse Width:

1. Under "STIMULUS SETTINGS", press the "PW" button. You will notice a flashing block over the number 0 in 100us.



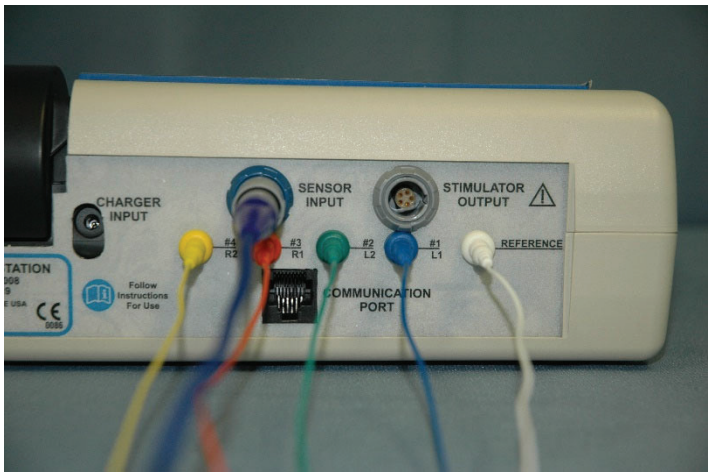
2. To increase pulse width, use the up arrow (▲).
    a. Maximum pulse width setting is 200us.
3. To decrease pulse width, use the down arrow (▼).
    a. Minimum pulse width setting is 20us.
4. When finished with the adjustments, press the "SELECT' button and the indicator will move to the next channel.
5. All four channels need to be set for 200us and the select button is pressed to have the indicator point to each channel.

Introduce the colored cables into the sterile field in the following order: green, orange, yellow and white. Connect in the following sequential order the alligator clamps to the silver pin on the designated electrodes;

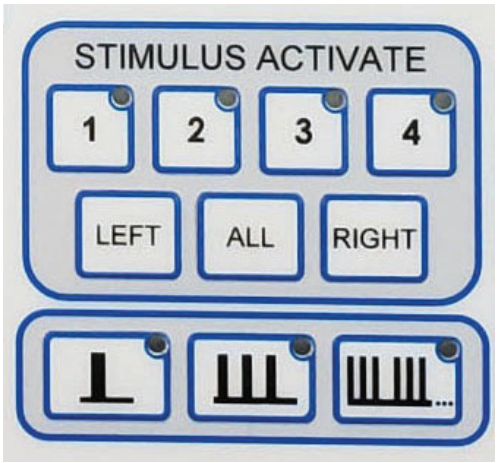
1. Blue to 1st left IM electrode
2. Green to 2nd left IM electrode
3. Orange to 1st right IM electrode
4. Yellow to the 2nd right electrode

5. White to the indifferent electrode

Connect each cable to the respective matching colored port on the NeuRx® Clinical Station.



Each lead is checked sequentially by depressing the number 1, 2, 3, 4 in order and noting readings of "❖" or "X". Then depress the "LEFT" button to stimulate the left hemi-diaphragm followed by the "RIGHT" button. Check all leads by pressing the "ALL" button. These buttons are found in the "STIMULUS ACTIVATE" section of the NeuRx® Clinical Station.



To pace all the leads, press the Pulse train button and then the "ALL" button. The NeuRx® Clinical Station will now be stimulating the entire diaphragm and the patient is now pacing at 12 breaths per minute (BPM). Ask the anesthesia team to run a cardiac rhythm strip while pacing to confirm no cardiac rhythm interaction.

You may request the anesthesia team to discontinue ventilation while the patient is being paced and note tidal volume on the anesthesia record. Then reinitiate ventilation, gently disconnect the clamps from the electrodes and turn off the NeuRx® Clinical Station. Cover the exiting electrodes with an appropriate sized dressing and secure with an occlusive dressing.

At the conclusion of the case, it is recommended that a chest x-ray be obtained to verify that no intra-abdominal CO_2 has entered into the chest cavity (capnothorax). If a capnothorax is present, it can be resolved with deep tidal volumes by Anesthesia [*deep breathing*] and, if clinically indicated, aspirated with a percutaneous catheter at the end of the surgery.

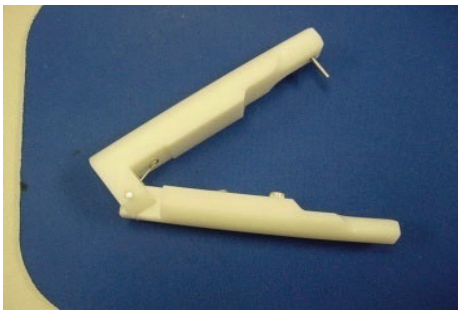
23.0 Blocking

Blocking is the final process of preparing the wires to allow connection to the NeuRx DPS® and its connection cable. Blocking can be done in the Operating Room or in Recovery.

[CAUTION: When performing this step, avoid pulling excess electrode from the exit site. Excessive externalized electrode from the exit site could lead to accidental electrode breakage.]

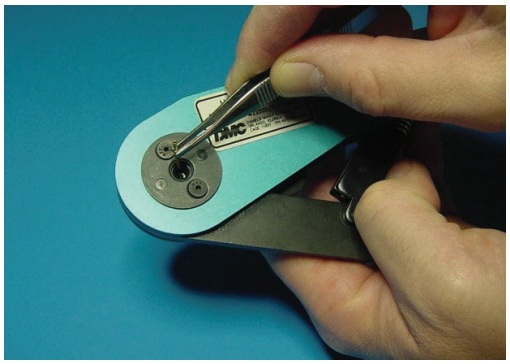
If covered, carefully remove gauze pad to view the electrode exit site and clean the exit site with an alcohol pad. Obtain the crimping tool, the socket pusher and the electrode connector kit (22-0005).

Crimping Tool

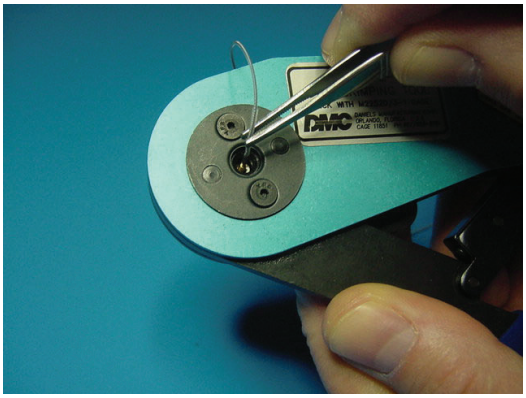

Socket Pusher

Electrode Connector Kit

1. Remove a gold pin from the electrode connector kit. Using tweezers, grasp the larger end of the gold pin and place the tapered end into the crimping tool.



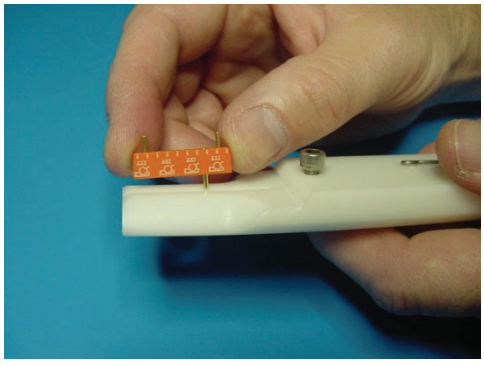
2. Using tweezers, gently insert the silver pin end of the electrode into the larger end of the gold pin that has been placed in the crimping tool.



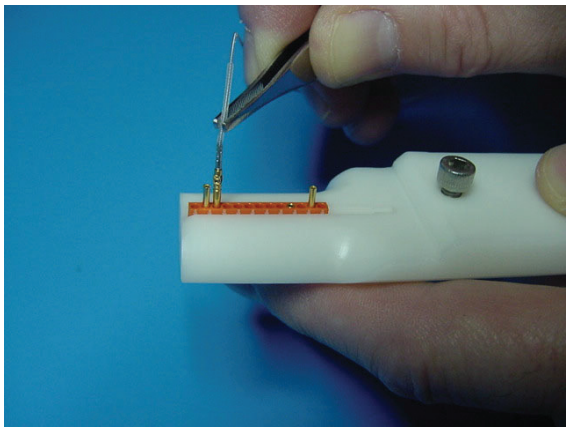
3. While holding the silver pin into the gold pin, firmly squeeze the handle of the crimping tool until it stops. Release handle and carefully remove crimped electrode from crimping tool

4. Repeat this process until a gold pin has been crimped on all exiting electrodes.

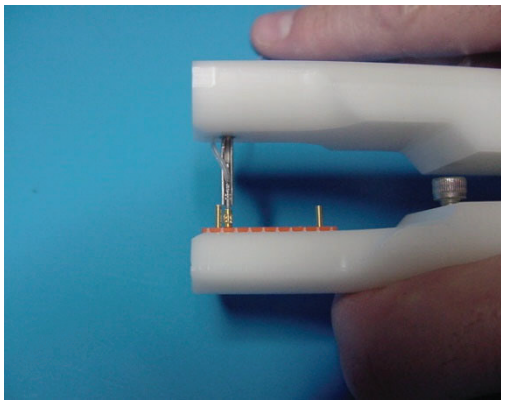
5. Place the electrode connector into the socket pusher and orient the electrode connector with the two gold pins visible as pictured above.

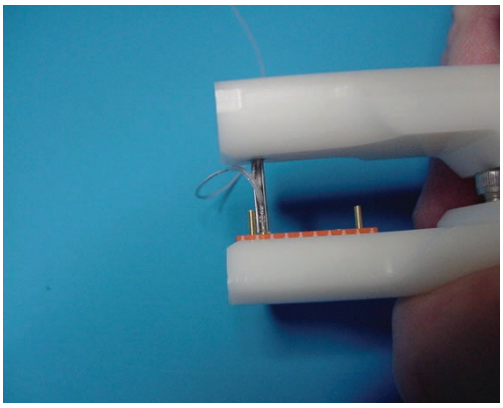


6. Starting with the most cephalad (superior) electrode, insert the electrode into the 3rd hole in the electrode connector.

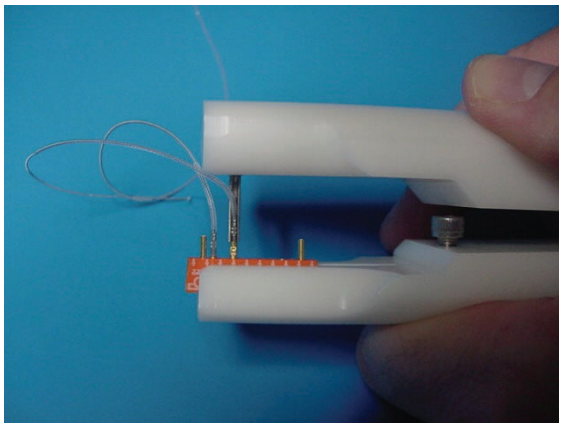


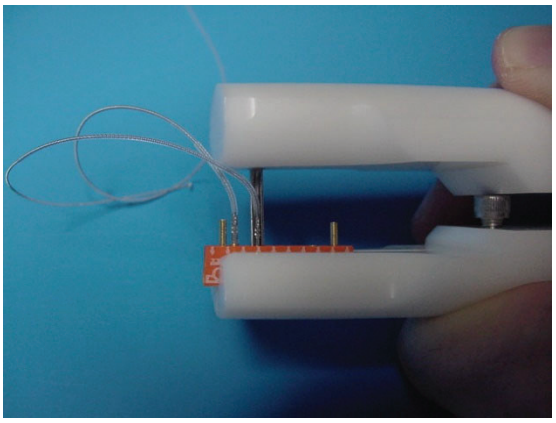
7. Gently close the socket pusher and line up the electrode into the slot of the pusher. Once lined up, firmly close the socket pusher.





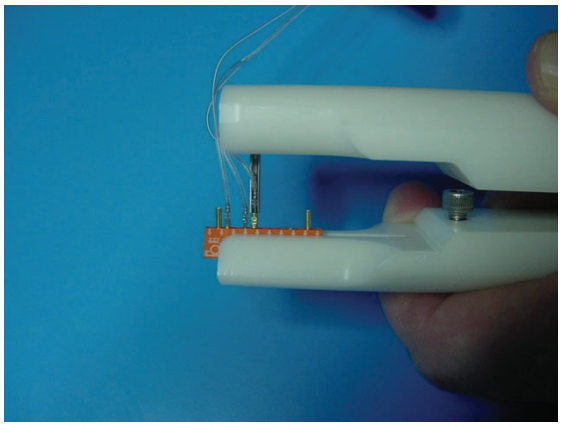
8. Select the next cephalad electrode and insert into the 5th hole in the electrode connector.

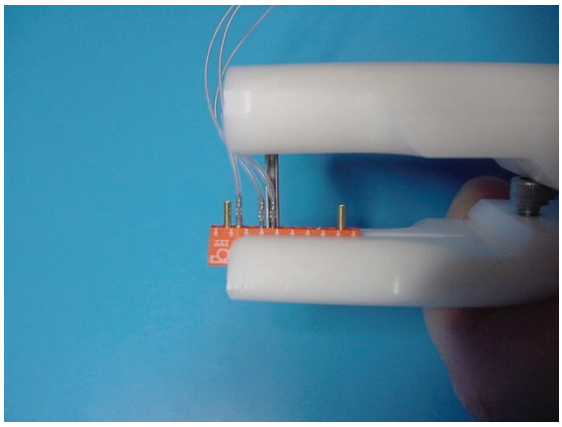




9. Gently close the socket pusher and line up the electrode into the slot of the pusher. Once lined up, firmly close the socket pusher.

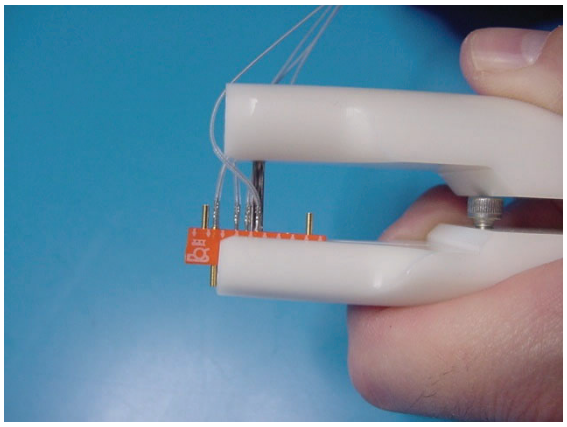
10. Select the 3rd cephalad electrode and insert into the 6th hole in the electrode connector.

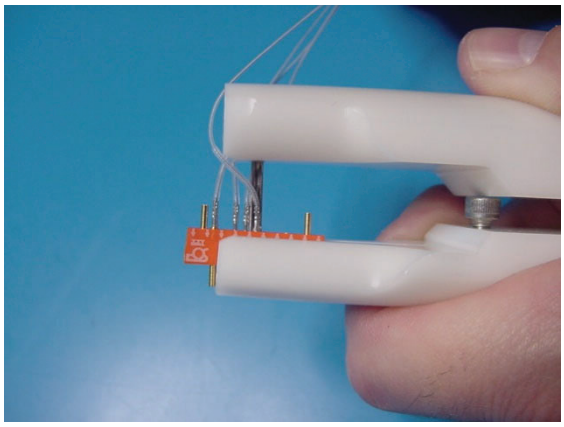




11. Gently close the socket pusher and line up the electrode into the slot of the pusher. Once lined up, firmly close the socket pusher.

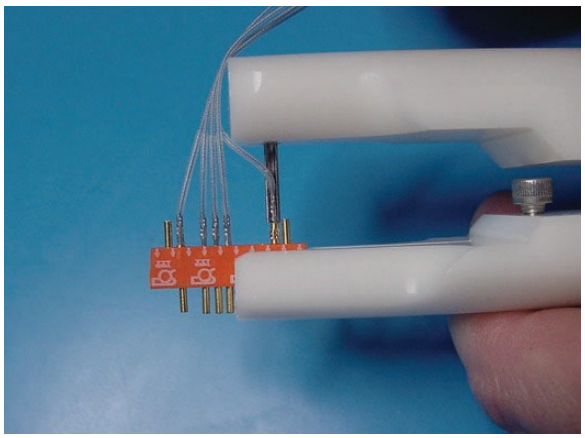
12. Select the 4th cephalad electrode and insert into the 7th hole in the electrode connector.

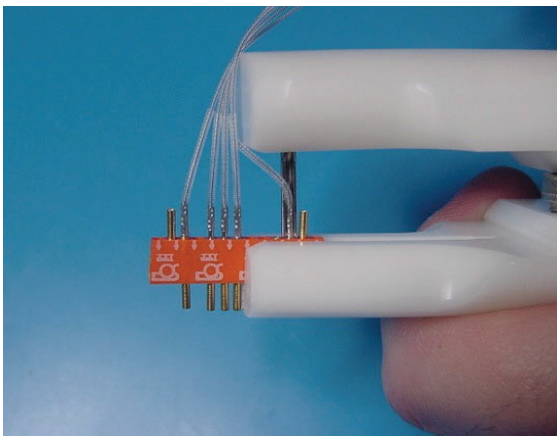




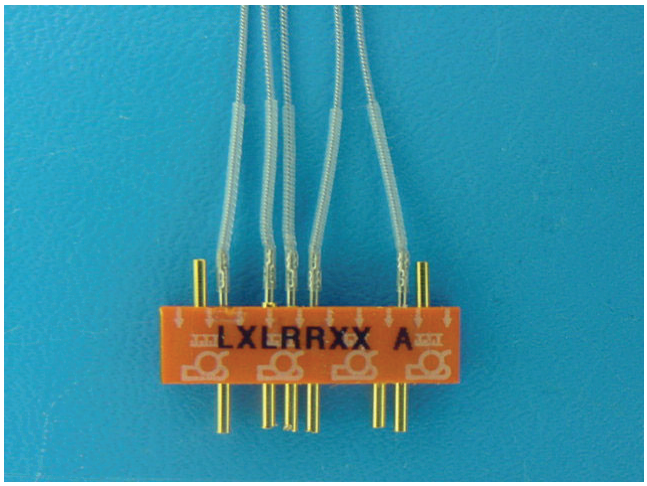
13. Gently close the socket pusher and line up the electrode into the slot of the pusher. Once lined up, firmly close the socket pusher.

14. Select the indifferent electrode and insert into the 11th hole in the electrode connector.





15. Gently close the socket pusher and line up the electrode into the slot of the pusher. Once lined up, firmly close the socket pusher.



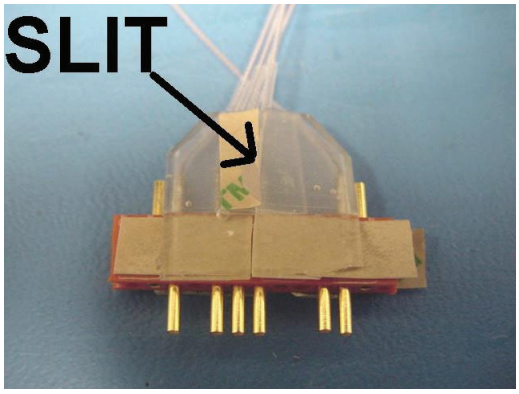
Assembled Electrode Connector

Carefully connect the patient cable to the electrode connector and perform a system check by using the NeuRx® Clinical Station at minimal settings. If an "X" is displayed in any channel, remove the identified gold pin from the electrode connector.

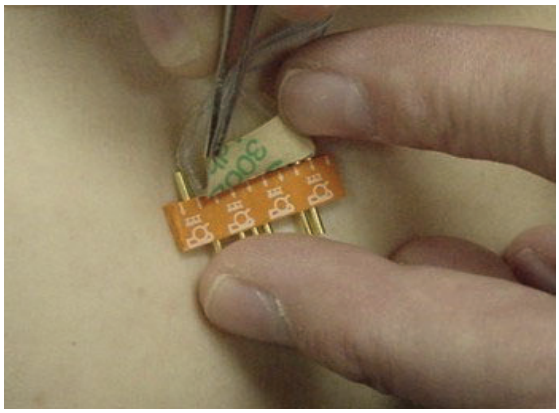
24.0 Apply Strain Relief Boot

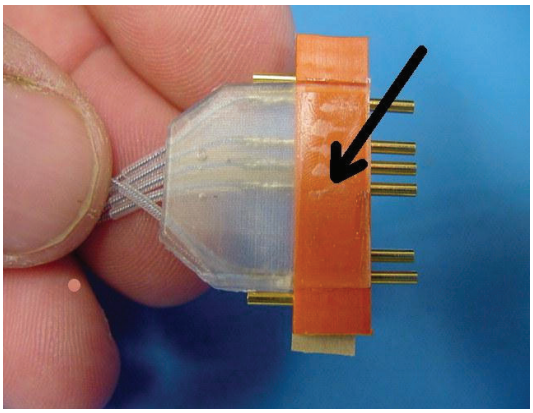
The strain relief boot (found in the Surgical Connector Kit, part 22-0028) is pre-slit along the center of one of the flat surfaces to aid placement over the electrode wires.

1. Gently open the SLIT on the strain relief boot and wrap around the electrode leads and then slide the boot over the electrode connector block.

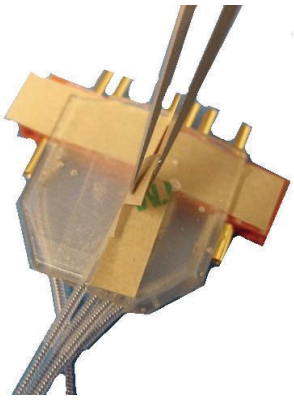


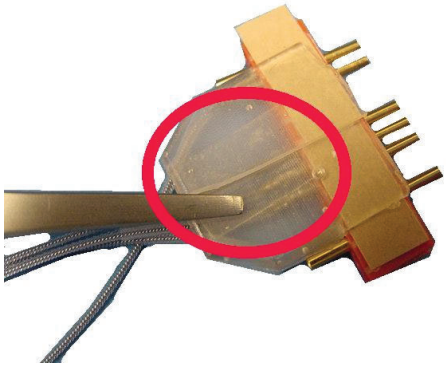
2. Turn the connector over (opposite of SLIT side) and hold the front flap of the boot up and remove the adhesive liner with forceps. Press the boot down firmly to the connector as shown.



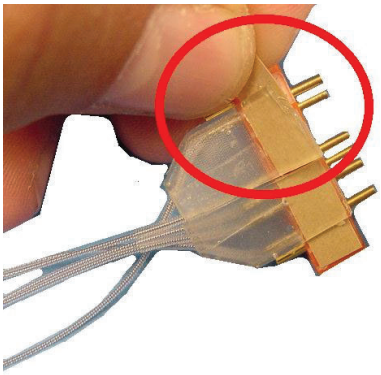


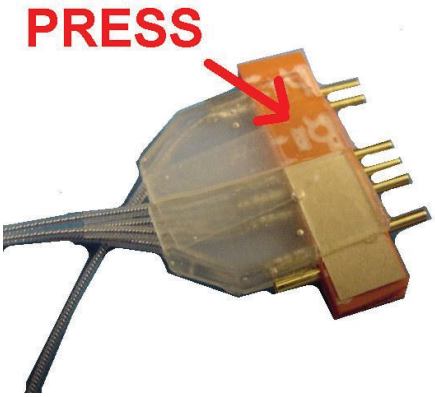
3. Turn the boot back over to SLIT side. Remove the adhesive liner on the SLIT and firmly press the flap down. DO NOT DAMAGE THE ELECTRODES WHILE DOING THIS.



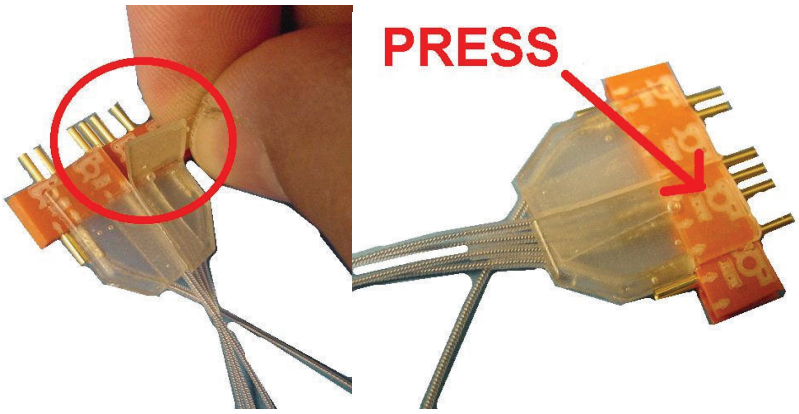


4. Remove the adhesive liner on the left side of the boot and press firmly to connector.

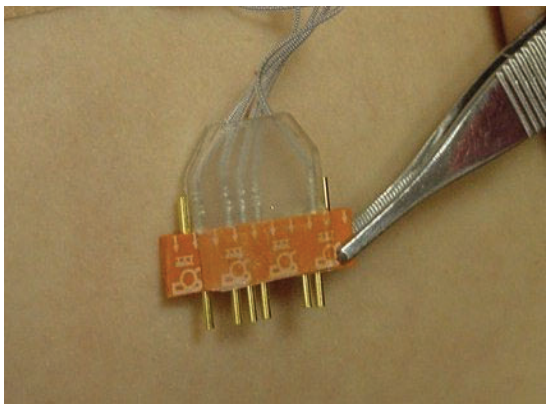
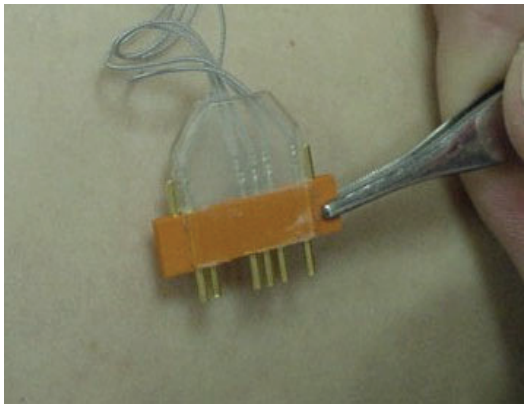




5. Remove the adhesive liner on the right side and press firmly on the connector as shown.



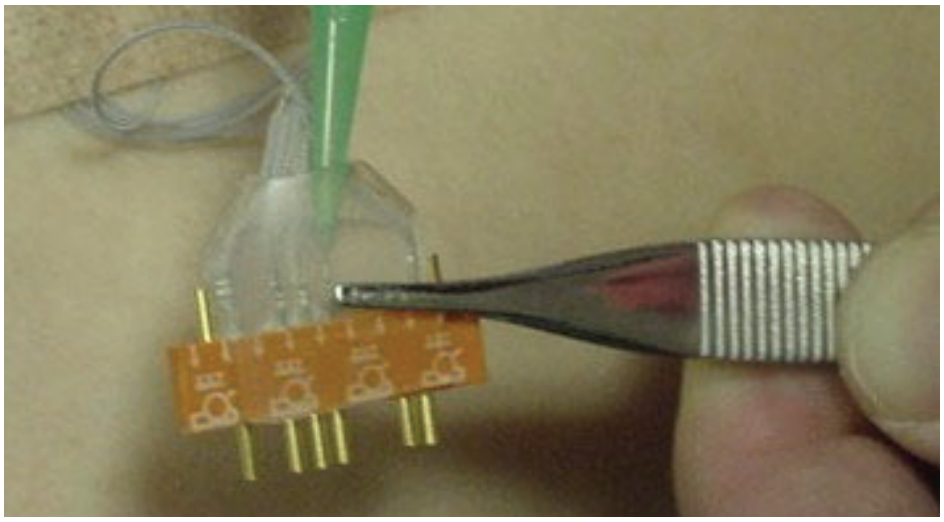
6. The assembled boot should appear as shown.

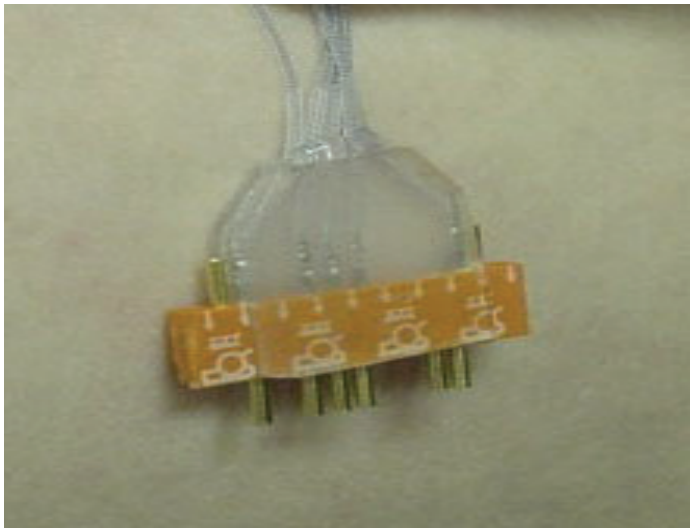
7. Remove the syringe filled with silicone adhesive from the kit and assemble grey tip to syringe. Save cap for resealing the tube after use.

8. Remove Plunger from bag and place in syringe. (Note: The Plunger is intentionally loose when placed in the syringe. It may fall out of syringe if turned upside down.)

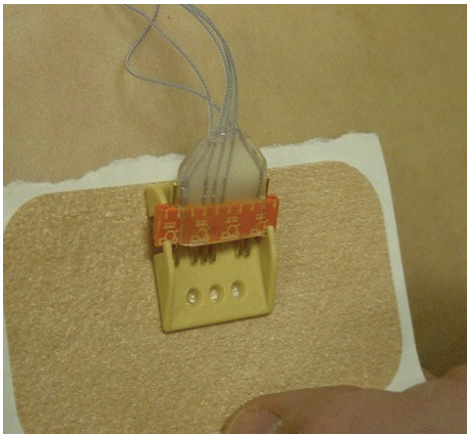
9. Gently insert grey tip of syringe into strain-relief boot all the way to the electrode connector block.

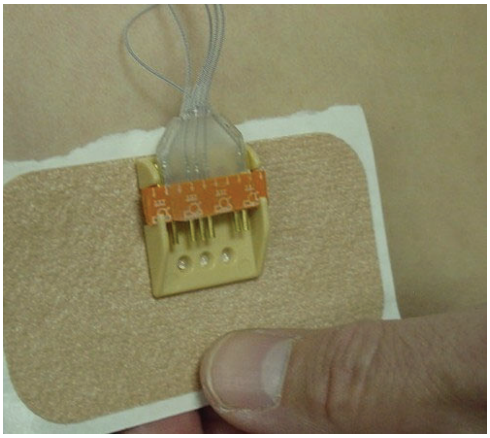


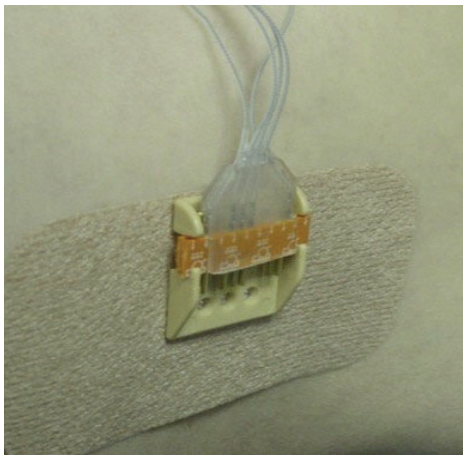
10. While holding the strain relief boot, **gently** back-fill the strain relief boot from the bottom ensuring that there are no voids or air bubbles. Remove any excess silicone at the exit of the boot.



11. Remove backing from the Connector Holder and secure to patient.







12. Position the electrode connector block into the connector holder to dry and position the 5 wires into a flat and straight alignment.

13. Cover the exposed electrodes with a gauze pad and secure with a water-proof adhesive dressing.

25.0 26. ESTABLISHING SETTINGS

Note: All settings are made at the discretion of the medical team. This information is provided as a reference point.

The NeuRx® Clinical Station is used to determine proper settings to provide stimulation to condition the diaphragm. Once these settings are determined, the NeuRx® Clinical Station will be used to program the patient's NeuRx DPS® for home use.

25.1 Changing Settings on the NeuRx® Clinical Station:

Place the NeuRx® Clinical Station into "STIMULATOR" mode by using the MODE button. Note that the NeuRx® Clinical Station will default to this mode and the selector will be on Channel 1 when it is turned on.

The NeuRx® Clinical Station will display default setting of AMP = 25mA, Pulse Width = 100µs, Respiration = 12 BPM, Inspiration Time = 1.1 seconds, Frequency = 20Hz, Pulse Ramp = 0.

To perform a system check of the electrodes, set the NeuRx® Clinical Station to the following starting settings: AMP = 10mA, Pulse Width = 100µs, Respiration = 12 BPM, Inspiration Time = 1.1seconds, Frequency = 14Hz, Pulse Ramp = 10.
NOTE: The adjustments are done as outlined below.

25.1.1 Adjusting Amplitude:

1. Under "STIMULUS SETTINGS", press the "AMP" button. You will notice a flashing block over the number 5 in 25mA.
2. To increase amplitude, use the up arrow (▲).
    a. Maximum amplitude setting is 25mA.
3. To decrease amplitude, use the down arrow (▼).
    a. Minimum amplitude setting is 5mA.
4. When finished with the adjustments, press the "SELECT' button and the indicator will move to the next channel.

25.1.2 Adjusting Pulse Width:

1. Under "STIMULUS SETTINGS", press the "PW" button. You will notice a flashing block over the number 0 in 100us.
2. To increase pulse width, use the up arrow (▲).
    a. Maximum pulse width setting is 200us.
3. To decrease pulse width, use the down arrow (▼).
    a. Minimum pulse width setting is 20us.
4. When finished with the adjustments, press the "SELECT' button and the indicator will move to the next channel.

Press the “SELECT’ button and the indicator will point to Channel 2.
Repeat the process for all four channels.

25.1.3 26.1.3 Adjusting Respiration Rate:

1. Under “STIMULUS SETTINGS”, press the “BPM” button. You will notice a flashing block over the number 1 in 12 BPM.
2. To increase respiratory rate, use the up arrow (▲).
    a. Maximum respiratory rate setting is 18 breaths per minute.
3. To decrease respiratory rate, use the down arrow (▼).
    a. Minimum respiratory rate setting is 8 breaths per minute.

25.1.4 Adjusting Inspiratory Time:

1. Under “STIMULUS SETTINGS”, press the “INSP” button. You will notice a flashing block over the “.” between 1.1
2. To increase inspiratory time, use the up arrow (▲).
    a. Maximum respiratory rate setting is 1.5 seconds.
3. To decrease inspiratory time, use the down arrow (▼).
    a. Minimum inspiratory time setting is 0.8 seconds.

25.1.5 Adjusting Frequency:

1. Under “STIMULUS SETTINGS”, press the “FREQ” button. You will notice a flashing block over the “0” in 20 Hz.
2. To increase the frequency, use the up arrow (▲).
    a. Maximum frequency setting is 20 Hz.
3. To decrease frequency, use the down arrow (▼).
    a. Minimum frequency setting is 5 Hz.

25.1.6 Adjusting Pulse Ramp:

1. Under “STIMULUS SETTINGS”, press the “RAMP” button. You will notice a flashing block over the “0”.
2. To increase the ramp, use the up arrow (▲).
    a. Maximum ramp setting is 10.
3. To decrease ramp, use the down arrow (▼).
    a. Minimum ramp setting is 0 Hz.

Each lead is checked separately by pressing the 1, then 2, then 3, then 4. The study results were obtained while conditioning the patient’s diaphragm at the highest setting at which the patient had no pain or discomfort. This setting is always less than the maximal allowed programmed settings of AMP of 25mA, pulse width of 200us and Frequency of 20 Hz.

You may check a lead multiple times by pressing the corresponding number on the NeuRx® Clinical Station. If no pain is noted, then the AMP can be segmentally increased.

If discomfort is noted, decrease the “AMP” of that lead until the discomfort is no longer noted or the AMP reaches 6 by performing the following:

1. Under “STIMULUS SETTINGS”, press the “AMP” button. You will notice a flashing block over the last number.
2. To decrease amplitude, use the down arrow (▼).

If discomfort continues to be felt, the pulse width is then decreased segmentally until discomfort is no longer noted or the pulse width reaches 60us by performing the following:

1. Under “STIMULUS SETTINGS”, press the “PW” button. You will notice a flashing block over the number 0 in 100us.
2. To decrease pulse width, use the down arrow (▼).

If discomfort is then felt then the Frequency is decreased segmentally by performing the following:

1. Under “STIMULUS SETTINGS”, press the “FREQ” button. You will notice a flashing block over the last number.
2. To decrease frequency, use the down arrow (▼).

This is repeated for all four electrodes and then combination of both right and left hemi-diaphragms are checked. When both electrodes are stimulated together the patient may feel discomfort or pain and the setting are again decreased.

The left and right hemi-diaphragm is now checked by depressing the “LEFT” and “RIGHT” buttons. You may check left and right multiple times by pressing the corresponding button.

Once settings have been determined on the NeuRx® Clinical Station, print the settings by pressing the “PRINT STIMULUS SETTINGS” button located below the printer.

26.0 Programming the NeuRx® External Pulse Generator (EPG)

Follow the steps outlined below:

1. Unscrew the battery cover on the back of the NeuRx® EPG and remove the battery.
2. Connect the Module Communication Cable to the communication port in the NeuRx® EPG.
3. Turn on the NeuRx® EPG by firmly pressing the two buttons at the same time and release. Allow the NeuRx® EPG to cycle a few times.
4. Press the “SEND STIMULUS SETTINGS” button. It is located left of the display screen on the NeuRx® Clinical Station.
5. Turn off the NeuRx® EPG by firmly pressing the two buttons at the same time and release.

27.0 Confirming Settings

Follow the steps outlined below:

1. Leave the Module Communication Cable attached to the NeuRx® EPG.
2. Turn the NeuRx® Clinical Station off, wait approximately 10 seconds and turn it back on. It will be in stimulator mode.
3. Press the MODE button on the NeuRx® Clinical Station until you reach the “PROGRAMMER” screen.
4. Turn on the NeuRx® EPG by firmly pressing the two buttons at the same time and release.
5. Press the “RETRIEVE STUMULUS SETTINGS” button. It is located left of the display screen on the NeuRx® Clinical Station.
    a. Settings will be transferred to the display on the NeuRx® Clinical Station.
6. Print the settings by pressing the “PRINT STIMULUS SETTINGS” button located below the printer.
7. Compare the two printouts for accuracy. If not the same, repeat steps in Programming the NeuRx® EPG.
8. Disconnect the communication cable from the NeuRx® EPG and replace the battery.
9. Replace the battery cover.

Appendix A: Summary of Clinical Studies

Summary IDE G920162 and data from patients implanted with the NeuRx device after HDE approval.

A one-armed pivotal clinical study was performed to establish a reasonable assurance of safety and effectiveness of NeuRx DPS® implanted via a laparoscopic surgical procedure. The NeuRx Diaphragm Pacing System is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but who lack control of their diaphragms (G920162). The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. It is indicated for use only in patients 18 years of age or older in the US.

This clinical study summary describes data collected in IDE G920162 as well as data from patients implanted with the NeuRx device after Humanitarian Device Exemption (HDE) approval in June 2008.

The data analysis of 3 cohorts is presented:

1. The primary cohort of 53 patients in the IDE trial (G920162)
2. A 106-patient cohort– comprised of 53 patients from the primary cohort pooled with 53 HDE patients in the secondary cohort (Onders et. al where the total n= 92, 39 of which were included in the IDE primary cohort)
3. A 196-patient cohort – 106 pooled patients plus 90 patients from 3 tertiary studies (the tertiary cohorts are comprised of additional HDE patients (n=40, n=31 and n=29).

These 5 groups of patients comprise the clinical population used in the statistical analyses. Of note, the clinical protocol notes that "p-values are provided for comparative purposes only, to update the original study report results, and not for labeling purposes per the Statistical Analysis Plan".

Effectiveness Data:

Primary Endpoint

Proportion of patients not requiring MV 4hrs/day. FDA agreed that this is a clinically meaningful endpoint. The performance goal was 45% and was based on the efficacy results of the Avery diaphragm pacing system.

Cohort 1

Table A.1: Primary Endpoint, Primary Analysis Cohort (n=53)

Event	% (n/N)	95% confidence interval	p-value*
Primary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day)	96.2% (51/53)	(87.0%, 99.5%)	<0.001

* Exact two-sided binomial test against performance goal of 45% (0.45)

The survival endpoint of the primary cohort was not identified as feasible to be analyzed in the original one-year follow-up at the time of the study. The survival analysis was added based on the follow-up at the time of Onders et al. 2018 publication, which was 18 years after the first patient was implanted in the primary analysis cohort. Thus, survival also appears to be improved with DPS although this was not a pre-specified endpoint.

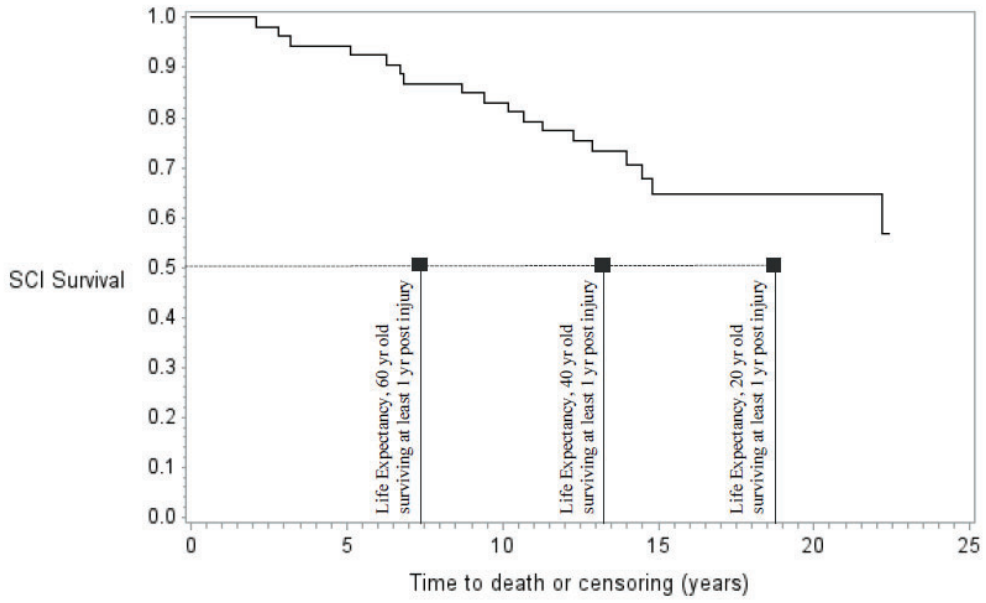


Figure A.1: SCI Survival (years since injury for Primary Analysis Cohort n=53)

Cohort 2

Table A.2: Primary Endpoint, Secondary Analysis Cohort (n=106)

Event	%(n/N)	95% confidence interval	p-value*
Primary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day)	89.6% (95/106)	(82.2%, 94.7%)	<0.001

* Exact two-sided binomial test against performance goal of 45% (0.45)

Cohort 3

Table A.3: Primary Endpoint, Secondary Analysis Cohort(n=196)

Event	%(n/N)	95% confidence interval	p-value
Primary endpoint (Proportion of subjects using the NeuRx DPS® without the assistance of a mechanical ventilator 24 hours a day)	92.2%	82.6%, 96.7	<0.001

Secondary Endpoint = Tidal Volume in Chronic Use

Cohort 1

Table A.4: Tidal Volume All Subjects

Characteristic	Mean ± SD (N) [Median] (IOR)	p-value (Vt vs basal requirements)
Basal requirement	**524.3 ± 146.1 (53) [518.01] (441.0,637.0)**	
Stimulated Vt	**745.6 + 217.7 (53) [700.0] (605.0,865.0)**	
Percentage of tidal volume over basal requirements (PTOVB)	**48.4 ±41.5 (53) [51.51] (26.1,68.1)**	**<0.001**

Cohort 2 = N/A

Cohort 3 = N/A

Secondary Endpoint = Use of NeuRx DPS® without MV 24hrs/day

An objective of the NeuRx therapy is to replace mechanical ventilation for patients on a chronic use basis; a surrogate secondary indicator of this objective is tidal volume (Vt) during chronic stimulation. Standard of care for ventilated patients indicates that the basal Vt requirements for an adult male are typically 7ml / kg of body weight and 6ml / kg for adult females. Due to ventilator circuit dead space, tracheotomy leakage, and duration/volume of speech concerns, spinal cord patients are typically mechanically ventilated at much higher settings than their basal Vt requirements.

The tables below display basal requirements, stimulated Vt, and the computed percentage of tidal volume over basal requirements (PTOVB) along with a hypothesis test against μ (PTOVB)=0 as provided in the original IDE Pivotal Study report; data are analyzed from the primary analysis cohort only (the IDE Pivotal Study) as this is the only source providing tidal volume data (Table A.5). p-values are provided for comparative purposes only, to update the original study report results, and not for labeling purposes per the Statistical Analysis Plan.

Cohort 1

Table A.5: Tidal Volume All Subjects

Characteristic	Mean ± SD (N) [Median] (IQR)	p-value (Vt vs basal requirements)
Basal requirement	524.3 ± 146.1 (53) [518.0] (441.0,637.0)	
Stimulated Vt	745.6 ± 217.7 (53) [700.0] (605.0.865.5.0)	
Percentage of tidal volume over basal requirements (PTOVB)	48.4 ± 41.5 (53) [51.5] (26.1,68.1)	<0.001

Further analysis by gender, shows sufficient PTQYB performance in both males (Table A.6) and females (Table A.7).

Table A.6: Tidal Volume Males

Characteristic	Mean ± SD (N) [Median] (IOR)	p-value (Vt vs. basal requirements)
Basal requirement	575.4 ± 119.1 (41) [556.0] (476.0,058.0)	
Stimulated Vt	793.9 ± 219.4 (41) [800.0] (660.0,900.0)	
Percentage of tidal volume over basal requirements (PTOVB)	42.0 ± 41.5 (41) [47.5] (11.8,61 9]	<0.001

Table A.7: Tidal Volume Females

Characteristic	Mean ± SD (N) [Median] (IOR)	p-value (Vt vs basal requirements)
Basal requirement	349.8 ± 80.2 (12) [336.0] (300.0,373.5)	
Stimulated Vt	580.4 ± 102.5(12) [602.5] (507.5,650.0)	
Percentage of tidal volume over basal requirements (PTOVB)	70.1 ± 35.2 (12) [65.5] (47.1,84.7)	<0.001

Use of NeuRx DPS® to breathe without the assistance of a mechanical ventilator for 24 continuous hours a day

As with the primary endpoint, the primary analysis cohort for this secondary endpoint is defined to be data collected from the Primary Study, for which 58.5% (31/53) of subjects achieved at least 24 hours daily use (Table A.8). A two-sided 95% confidence interval is provided for descriptive purposes, but no formal statistical test is conducted, in keeping with the Statistical Analysis Plan. Ultimately, this represents full independence from mechanical ventilation and ability to support natural negative pressure respiration for the 58.5% of patients that have reached this endpoint.

Table A.8: 24 hour/daily use - Primary Analysis Cohort (n=53)

Event	%(n/N)	95% confidence interval
Secondary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator 24 hours a day)	58.5% (31/53)	(44.1%,74.9%)

Cohort 2

Table A.9: Secondary Endpoint (24 hr/daily use), Secondary Analysis Cohort (n=106)

Event	%(n/N)	95% confidence interval
Secondary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator 24 hours a day)	56.6% (60/106)	(46.6%, 66.2%)

Cohort 3

Table A.10: Secondary Endpoint (24hr/daily use), Secondary Analysis Cohort (n=196)

Event	%(n/N)	95% confidence interval
Secondary endpoint (Proportion of subjects using the NeuRx DPS® without the assistance of a mechanical ventilator 24 hours a day)	52.7%	(36.2, 68.6)

Safety Endpoints:

In no case was the patient required to return to the operating room for device repair. In the IDE Pivotal Trial, none of the commonly tracked peri-operative complications, including venous thrombosis, pulmonary embolus, wound infections, and pulmonary infections were reported. The most common peri-operative adverse event was a capnothorax, which is a common side- effect of laparoscopic surgery, was tracked and involved 21 out of 54 patients (39%).

In the IDE Pivotal Trial there were no perioperative deaths.

This device met the predefined primary endpoint by allow 90% of patients to breath without a ventilator for at least four hours per day. A secondary endpoint of breathing without a ventilator for 24 h per day was achieved in 50% - 60% of subjects.

A. Study Design

IDE Pivotal Study– G920162

The Pivotal Study of the NeuRx DPS® system was conducted at 5 investigational sites as a prospective, non-randomized, multi-center study to demonstrate the safety and effectiveness of the NeuRx device utilizing a patient as their own control. Patients were implanted between March 2000 and March 2008.

The primary effectiveness endpoint was defined as use of the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. It was reported

that 96.2% (51/53) of patients achieved at least 4 continuous hours daily use compared to the performance goal (PG) of 45% ($p<0.001$). In addition, it is found that 58% of subjects achieved at least 24 hours daily use.

Safety: There was no specific safety hypothesis, but a detailed summary of all adverse events (AEs) was provided. The safety of the NeuRx device was comparable to patients on mechanical ventilation with no apparent increase due to the device. Survival rates of patients using the NeuRx device were at least comparable if not better than patients on mechanical ventilation.

The clinical study data was collected and analyzed per the protocol. The clinical data were collected on the final design of the device except changes enumerated in Supplements since approval of H070003. The study population selected matches the device IFU and the endpoints are clinically relevant.

According to the study results described in the PMA (P200018), there is strong evidence that the NeuRx device can benefit SCI patients in terms of breathing without the assistance of a mechanical ventilator for at least 4 continuous hours a day.

Data Safety Monitoring

A Data and Safety Monitoring Board consisting of a pulmonologist, spinal cord rehabilitative specialist and surgeon was formed to regularly review study progress and adjudicate adverse events. Members of the DSMB were not employees or major shareholders of Synapse, Inc. and did not participate as investigators. The committee's purposes were to review and classify all serious adverse events including death occurring in treated patients, to determine if the rate of adverse events was acceptable, to evaluate data analysis results, and to provide related advice to Synapse, Inc., on study management and progress. Meetings were held on a basis determined appropriate for this study.

1. Clinical Inclusion and Exclusion Criteria

Enrolment in the NeuRX -RA/4 Neuromuscular Stimulator study was limited to patients who met the following inclusion criteria

Inclusion:

- Age 18 years or older
- Cervical spinal cord injury with dependence on mechanical ventilation
- Clinically stable following acute spinal cord injury
- Bilateral phrenic nerve function clinically acceptable as demonstrated with EMG recordings and nerve conduction times
- Diaphragm movement with stimulation visible under fluoroscopy
- Clinically acceptable oxygenation on room air (>90% 02 saturation)
- Hemodynamically stable

- No medical co-morbidities that would interfere with the proper placement or function of the device
- Committed primary caregiver
- Negative pregnancy test in females of child-bearing potential
- Informed consent from patient or designated representative

Patients were not permitted to enroll in the NeuRX -RA/4 Neuromuscular Stimulator study if they met any of the following exclusion criteria:

- Co-morbid medical conditions that preclude surgery
- Active lung disease (obstructive, restrictive or membrane diseases)
- Active cardiovascular disease
- Active brain disease
- Hemodynamic instability or low oxygen levels on room air
- Hospitalization for, or a treated active infection, within the last 3 months
- Significant scoliosis or chest deformity
- Marked obesity
- Anticipated poor compliance with protocol by either patient or primary caregiver
- Currently breastfeeding

The study population matches the device intended use.

2. Follow-up Schedule

The 52 subjects, and their caregivers, agreed to a follow-up schedule that could last 12 months. Follow-up was scheduled on subjects who had not achieved steady state use of the system at 3 months, 6 months, and 12 months.

Once a subject achieved steady state use of the system, follow-up was performed on an as-requested basis or at the discretion of the Investigator. Postoperatively, following the implant procedure, conditioning was started when patients were stable after surgery and when it was convenient for the patient's caregiver. Each electrode was characterized over the range of stimulus parameters using the Clinical Station. The objective parameters after initiation of stimulation measured during the study included tidal volumes which were recorded with a calibrated Wrights Spirometer and oxygen saturation was monitored with a pulse oximeter. It should be noted that the tidal volumes were measured with the patient's tracheotomy, which in many cases was a cuffless tracheal tube. This means that tidal volumes recorded (and subsequently reported in the results) with the Wrights Spirometer were lower than the actual inspired air volume due to air leaks around the patient's stoma and through their upper airway. An EKG rhythm strip was recorded at maximal stimulus parameters to assure that there was no capture of the cardiac waveform. Initial parameter settings were determined, and the external stimulator was programmed. Initial conditioning sessions were performed while the patient was at the hospital to assure the patient and their caregivers understood and were comfortable with the operation of the DPS. The patient returned home and logged his/her use of the NeuRx DPS® and the improvement in

tidal volume as determined with the Wrights Spirometer. Pulse oximetry and a rank scale indication of respiratory effort were recorded along with any comments with each use of the DPS.

All patients were scheduled to return for follow-up examinations during the initial weeks of DPS use, the clinical team assessed the patient's progress on a weekly basis by reviewing the log sheets and making any changes to parameters as necessary. Log sheets were maintained until the patient had reached, or was capable of, full time use. If the patient had not reached a steady-state plateau or full time use of the system by 3, 6, and 12-month intervals post-surgery, the electrodes were characterized again. Once the patient had achieved full time use of the DPS or was using it at a level that was consistent with their desired level of activity, they were free to use the system as desired.

Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Additional Supporting Studies

After ten years of real-world experience under the HDE, additional sources of evidence of effectiveness have been independently published which support the use of DPS. Each of these supporting studies, designated as studies #2 - #5 are summarized in Table A.11. These studies were used to support the efficacy endpoints as described below.

Table A.11: Published Supporting Data of NeuRx DPS®

Study ID	**Study Population Study Type Subject Number Characteristics**	**Efficacy Results as Published**	**Safety Results as Published**
Study #2 - Onders et al. (2018)	Single center, single arm, open label, retrospective review N=92 39 IDE and 53 HDE tetraplegic patients with viable phrenic nerves and diaphragm muscles; including pediatric pts. (15%). Mean time on MV = 47.5m (range 6d-25y)	• 88% (81/92) achieved 4 hours of DPS pacing • 60.8% (56/92) used DPS 24 h/d • 5 pts (5.4%) had full recovery of volitional breathing • Five patients (5.4%) were not successfully weaned from MV • Subgroup analysis showed a trend that earlier DPS implantation leads to a greater number of patients utilizing DPS for 24 hours.	• Median survival was 22.2 years (95% CI 14.0 - not reached) with only 31 deaths. • 4/5 (80%) of patients unable to be weaned from MV died a mean of 9.9 months post-injury. • 17 patients with causes of death available, none were attributable to the device.

Study #3 - Kerwin et al (2018)	Single center, single arm, retrospective matched cohort analysis (NeuRx DPS® vs MV). N=40 HDE patients with early DPS implants vs 61 matched pts w/o DPS implant. Mean time to implant=14d	• The DPS patients that developed VAP (26/40) had significantly shorter vent days as compared to the control patients that developed VAP (39/61): 24.5 ± 15.2d vs. 33.2 ± 23.3d; p=0.05	Mortality and length of hospital stay were significantly higher in the control group: • Mortality significantly higher in the MV group (15% vs 3%; p=0.04) • Length of hospital stay significantly higher in the MV group (65±61 vs 43±24d; p=0.03)

Study #4 - Lammertse et al (2016)	6 centers, prospective experience report of SCI and implanted with DPS: N=31 patients, (predominantly commercial HDE); with follow-up data on 28 pts. Outcomes collected 2011-2016 on pts., 78% had C1 or C2 SCI, with implants 2007-2014, and mean implant time post-injury: 4.5y (<1 month to 28y)	• 24/26 pts. (86%) were still using DPS at the lime of the follow-up (mean 16h/d) • 7/28 pts. (25%) were pacing 24h/d • 4/28 pts. (14%) were not pacing due to: "medical issues", adverse reaction to pacing, shoulder pain, or need for pressure support via ventilator • Patients (n =28) initiated DPS at mean of 2.5d and a median of 1d (range 0-7d) post-implant. Achieved pacing for 6h/d after a median of 7d (range 0-60d) and 24h/d after a median of 5d (range 0-30d). Mean follow-up: 3.2y (range 15d-7.4y)	Device-related adverse effects reported were. • infection Issues at the electrode wire exit site (17%), • pain with pacing (14%), and • electrode wire issues involving hospitalization (13%)
Study #5 - Posluszny et al (2014)	10 centers, retrospective analysis of SCI pts. implanted with DPS. N=29 patients; 22 implanted, 7 nonresponsive diaphragms. Patients included at median 33d post injury (range 3-112d)	• 73% (16/22) implanted were free of MV at a mean of 10.2d after DPS • 36% (8/22) had complete recovery of respiration and DPS wires were removed	• 1 patient, withdrawal of care and death • 3 (14%) partial wean and/or use with MV

3. Clinical Endpoints

Safety Endpoints:

- Assessment of device-related adverse events in the NeuRx DPS® population, compared to a similar patient population without DPS use.
- All-cause mortality in the NeuRx DPS® population, compared to a similar patient population without DPS use.

Primary Effectiveness Endpoint:

The primary effectiveness endpoint was defined as use of the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. This endpoint is reported as the proportion of subjects achieving the endpoint and assessed using binomial methods for the primary cohort (IDE population n=53), the secondary cohort of the pooled data between the Primary cohort and Onders HDE patients (n=106), and then using mixed models for the meta-analysis of all data sources (n=196).

The three hypothesis tests specified above are tested hierarchically in the order indicated, with the analysis of the primary cohort alone first, the pooled secondary cohort second, and the meta-analysis results from all data sources third. Each test was only performed if the prior test in the sequence met statistical significance against the performance goal at the 0.05 two-sided level, thereby preserving overall Type I error at 0.0.

Secondary Effectiveness Endpoints:

- Tidal volume (VT) during chronic stimulation is a secondary indicator of the objective to replace mechanical ventilation for patients on a chronic use basis. Standard of care for ventilated patients indicates that the basal VT requirements for an adult male are typically 7ml / kg of body weight and 6ml / kg for adult females.
- Use of NeuRx DPS® to breathe without the assistance of a mechanical ventilator for 24 continuous hours a day.

B. Accountability of Study Cohort

The IDE (G920162) that was in progress at the time of HDE submission, and used in support of the HDE approval, continued with enrollment up to the inclusion of 50 subjects enrolled at U.S. centers. Three additional subjects were implanted (all three included in the HDE analysis) at investigational sites outside of the U.S. and one subject was a compassionate use patient that was approved by FDA with instructions from FDA that "data from this patient should be clearly distinguished from the study data" and not combined. Thus, a total of 54 subjects gave informed consent and the analysis cohort had 53 subjects. One subject, in the analysis cohort, had an unresponsive diaphragm at implant and thus never actively used the device. The remaining 52 subjects, and their caregivers, agreed to a follow-up schedule that could last 12 months. Follow-up was scheduled on subjects who had not achieved steady state use of the system at 3 months, 6 months, and 12 months. Once a subject achieved steady state use of the system, follow-up was performed on an as-requested basis or at the discretion of the Investigator. All subjects were allowed to continue device use once HDE approval was received.

Table A.12: Primary Cohort Demographics and Injury History

Period	Analysis Cohort	Active During Period	Reached 4 continuous hour milestone	Exclusion or Withdrawal	
Enrolled	54	54	—	1	1 compassionate use excluded
Implanted	53	52	—	1	1 unresponsive diaphragm at surgery

3 months	53	52	36	0	
6 months	53	52	43	0	
12 months	53	50	50	2	Two deaths between 6 & 12 months

One subject suspended conditioning because of a malfunctioning baclofen pump. Conditioning resumed but the subject did not achieve 4 continuous hours by the date of HDE approval.

One subject achieved 4 hours of use after six months but died before 12 months.

Table A.13: Deaths reported during the IDE study, prior to HDE approval

Subject	Age at Injury (years)	Date of Implant	Date of Death	Months After Implant	Months After Injury
01-03	42.7	2/28/03	10/10/04	19.3	112.4
01-15	20.3	2/16/05	8/28/05	6.4	167.9
01-17	69.7	5/18/05	3/24/06	10.2	38.5
01-20	14.6	1/23/06	10/10/07	20.6	73.3

Data analysis of 3 cohorts is presented:

1. the primary cohort of 53 patients in the IDE trial (G920162)
2. 106 patients – 53 from the primary cohort pooled with 53 HDE patients in the secondary cohort (Onders et. al where the total n= 92, 39 of which were included in the IDE primary cohort)
3. 196 patients – 106 pooled patients plus 90 patients from 3 tertiary studies (the tertiary cohorts are comprised of additional HDE patients (n=40, n=31 and n=29).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. Per the National Spinal Cord Injury Statistical Center (NSCISC), the average age at injury has increased from 29 years during the 1970s to 43 since 2015. About 78% of new SCI cases are male. Vehicle crashes are the most recent leading cause of injury, closely followed by falls. Acts of violence (primarily gunshot wounds) and sports/recreation activities are also relatively common causes for SCI. About 24% of injuries have occurred among non-Hispanic blacks, which is higher than the proportion of non-Hispanic blacks in the general population (13%).

Table A.14 provides the consolidated values for the demographics and injury history of the primary cohort (the IDE Pivotal Study). On average, 65.1 months had elapsed from injury to implant, and the mean age at the time of injury was 30.6 years. The most frequent causes of injury were motor vehicle accident and sporting activities, each occurring 37.7% (20/53) of

the time. The most common level of injury was C2, with 45.3% (24/53) of cases, followed by C1/C2 with 30.2% (16/53).

Table A.14: Primary Cohort Demographics and Injury History

Characteristic	Mean ± SD (N) [Median] (IQR) or % (n/N)
Age at implant	36.1 ± 16.9 (52) [28.4] (22.6,50.5)
Gender Female Male	 22.6% (12/53) 77.4% (41/53)
Age at injury	30.6 ± 18.6 (52) [23.2] (17.9,43.6)
Time from injury (months)	65.1 ± 81.0 (53) [28.3] (12.1,83.3)
Cause of injury Assault Bicycle Fall Industrial Meningitis MVA SP. Infarct Sports TM	 1.9% (1/53) 1.9% (1/53) 13.2% (7/53) 1.9% (1/53) 1.9% (1/53) 37.7% (20/53) 1.9% (1/53) 37.7% (20/53) 1.9% (1/53)
Level of injury C1 C1/C2 C2 C2/C3 C3 C3/C4 C4 C4/C5	 7.5% (4/53) 30.2% (16/53) 45.3% (24/53) 1.9% (1/53) 5.7% (3/53) 5.7% (3/53) 1.9% (1/53) 1.9% (1/53)

Table A.15 displays subject demographics and injury history for the secondary cohort (Onders et al.). Of the 92 patients implanted, 39 were included in the IDE primary cohort; 53 HDE patients were analyzed as part of the pooled secondary cohort. Table 15 information is restricted to the 53 HDE patients.

Table A.15: Onders et al. Demographics and Injury History

Characteristic	Mean ± SD (N) [Median] (IQR) or % (n/N)
Age at implant	29.1 ± 17.8 (53) [25.0] (17.0,40.0)
Gender Female Male	 24.5% (13/53) 75.5% (40/53)
Age at injury	26.3 ± 18.8 (53) [23.0] (16.0,38.0)

Characteristic	Mean ± SD (N) [Median] (IQR) or % (n/N)
Time from injury (months)	35.9 ± 54.2 (53) [13.9] (4.3,49.6)
Cause of injury	
Crush	5.7% (3/53)
Electrocution	1.9% (1/53)
Fall	15.1% (8/53)
Forceps Delivery	3.8% (2/53)
GSW	13.2% (7/53)
MVA	50.9% (27/53)
Sports	9.4% (5/53)
Level of injury	
C1	7.5% (4/53)
C1-2	13.2% (7/53)
C1-4	1.9% (1/53)
C2	17.0% (9/53)
C2-3	11.3% (6/53)
C2-4	1.9% (1/53)
C3	13.2% (7/53)
C3-4	5.7% (3/53)
C3-7	1.9% (1/53)
C4	1.9% (1/53)
C4-5	9.4% (5/53)
C5	1.9% (1/53)
C5-6	3.8% (2/53)
C5-7	3.8% (2/53)
C6	1.9% (1/53)
C6-7	3.8% (2/53)

D. Safety and Effectiveness Results

1. Safety Results

Safety of the Primary Cohort

Adverse Events

There were 165 adverse events recorded during the study, from the first patient implant on 3/6/2000 until the study patients were converted to HDE patients with the approval of the HDE on 6/17/2008. Thirty-eight (38) of the 54 implanted patients (including the compassionate use patient that is excluded from the efficacy analysis) had adverse events recorded. Thus, 16 of the 54 patients had no adverse events recorded during the study. There were 72 device related adverse events reported in 35 patients. Thus, 19 of the 54 patients had no device related adverse events. Of the 72 device related events, 30 were due to equipment malfunctions (external lead breaks or stimulator malfunctions) and another 21 were due to procedure related capnothorax, which is a side-effect of laparoscopic surgery and discussed in more detail below.

Eliminating those categories, 11 patients had device related adverse events.

Table A.16 lists the adverse events for patients in the primary cohort. Device related events are identified and placed into categories with respect to being device related, unanticipated or serious adverse events. There were four deaths during the study, none of them were device related. There was no device related serious adverse events (SAEs). There were 23 non-device related SAEs with several of them related to a root incident. With the exception of the deaths, the SAEs occurred in 5 patients. One patient had acute polynephritis that was reported with three additional SAEs at the same time, including elevated temperature, chest pain, and blood around the tracheostomy. Another patient had recurring pneumonia, reported six times over the course of eight months, also had an elevated temperature and UTI reported as SAEs at the same time. All of the SAEs had resolved by the end of the study.

There were 10 unanticipated adverse device events in 5 patients. The events were temporary spasms, elevated temperature, low VT O2, difficulty eating with device and interference with cardiac pacemakers.

Cohort 1 =

Table A.16: Adverse Event Listing for Primary Cohort

Adverse Event (AE)	# Events	Anticipated Device Related AE	# Affected Patients	UADE	SAE	Device Related SAE	% of Patients (n=54)
Capnothorax	21	21	21	0	0	0	39%
Broken External Wire	12	12	7	0	0	0	13%
External Equipment Failure	10	10	8	0	0	0	15%
UTI	10	0	7	0	2	0	13%
Broken Anode	8	8	6	0	0	0	11%
Upper Respiratory Infection	9	0	5	0	0	0	9%
Temporary Spasms	5	0	5	2	0	0	9%
Elevated Temperature	8	0	5	1	2	0	9%
Pneumonia	11	0	4	0	10	0	7%
Pain Discomfort with device	4	4	3	0	0	0	6%
Pain/Discomfort no device use	3	0	3	0	0	0	6%
Aspiration	11	11	3	0	0	0	6%
Low V_T, O_2	5	0	3	5	0	0	6%
Pressure Sore	4	0	3	0	0	0	6%
Increased Secretions	3	1	3	0	0	0	6%
Airway Obstruction	2	2	2	0	0	0	4%
Localized Infection	3	3	2	0	0	0	4%
Redness or swelling	4	0	2	0	0	0	4%
Autonomic Dysreflexia	3	0	2	2	0	0	4%
Death (while device not in use)	2	0	2	0	2	0	4%
Death (with device in use)	2	0	2	0	2	0	4%

Device related SAE = 0

Deaths with device = 0

Adverse events (AEs) or outcomes are generally related to the device itself, the use of the device or procedure to use the device and to anesthesia or sedation to use the device. Events may likely be confounded by, and attributed to, other comorbidities or treatment modalities.

Cohort 2 =

Median survival = 22.2 yrs. 4/5 not weaned died at mean 9.9 mos.

Device related deaths = 0

Safety information in the Secondary Cohort is limited to mortality as a listing of adverse Events was not part of the published information. Of the 53 patients implanted, there were 15 deaths (28%) which is not an unexpected rate for SCI patients who require mechanical ventilation.

Cohort 3 =

Adverse events not meta-analysed as data was incomplete. 1 study reports 17% wire infection rate, 14% pain with pacing, and 13% hospitalized due to wire issues.

There were 16 patients that had no adverse events reported. There were 84 device related adverse events recorded in 35 patients. The most frequently occurring adverse event recorded, in 21 patients, was a capnothorax at the time of implantation.

After the surgical related events of capnothorax and interference with cardiac pacemaker (which was programmed around with lower non-interfering settings), the adverse event of aspiration was the most frequent occurring.

There were 81 adverse events not related to the device or procedure recorded in 20 patients.

Complaints, post-approval of HDE (H070003):

Over the five years period of Sept 1, 2015, to August 31, 2020, there were a total of 547 patients implanted. During this period, there were ten MDR's filed with FDA related to patients implanted under H070003. There was a total of 182 total complaints from implanting sites or patients implanted during this period. In total 84% of the patients did not register any complaints over the five-year period, with 87% of SCI patients and 71% of off-label patients not having complaints. The majority of complaints occur in the first twelve months after implant. During the first year (day 0 – 360), there was a total of 67 complaints in 57 different patients. That represents 10.4% of the patient population with a complaint during the first year. Focusing on complaints that were deemed to be medical device reportable adverse events there were nine events in the five-year sample with an MDR for 1.6% of the patient population.

Thus, given the large sample of post-approval patients, there does not appear to be any indication of a discrepancy with the primary IDE cohort in terms of an increase in events in

the first-year post-implant or in subsequent years. There also is no indication, in the complaint data, of a wear-out mechanism over time with use of the device.

Adverse effects that occurred in the PMA clinical study:

The table below provides the data comparison of a Standard of Care surgical procedure population with the primary cohort in the DPS study. The literature reference for the Standard of Care population is identified in the Source column of the table. The Comparative Population column provides the data for the identified Adverse Event from the Source literature. In all cases, the incidence rate of the adverse event is lower for the DPS Primary Cohort than that published for the Comparative Population.

Table A.17: Adverse events, primary cohort to comparative populations

Adverse Event	DPS Primary Cohort	Comparative Population	Source
Capnothorax	21 / 53 (39.6%)	21 / 45 (47%)	Clements, 2000
Pneumonia	4 / 53 (7.5%)	1,968 / 3,019 (65.2%)[2]	2018 NSCISC Annual Report
		146 / 180 (81%)	Jaja, 2019
Aspiration	3 / 53 (5.7%)	15 / 46 (33%)	Ihalainen, 2017
Operative Mortality	0	2% - 7%	Johnson, 2007
Perioperative Complications			
Venous thromboembolism (VTE)[3]	0	21,630 / 4,107,430 (0.53%)	Stein, 2014
Pulmonary embolism (PE)	0	5,960 / 4,107,430 (0.15%)	Stein, 2014
Deep Vein Thrombosis (DVT)	0	16,610 / 4,107,430 (0.40%)	Stein, 2014
Wound infections	2 / 53 (3.8%)	1,579 / 9655 (16.3%)	Kagawa, 2019
Pulmonary infections	5 / 53 (9.4%)	430 / 3,084 (13.9%)[1] 3,019 / 14,094 (21.4%)[2]	2018 NSCISC Annual Report
Catheter/wire complications	5 / 53 (9.4%)	9 / 57 (16%)	Saval, 2010

[1] Reported as Diseases of the Respiratory System as cause of re-hospitalization during the first-year post-injury (Table 102)

[2] Reported as Diseases of the Respiratory System as the primary cause of death (Table 10)

[3] Venous Thromboembolism is PE and/or DVT

The laparoscopic approach described by Clements is very similar to that used by surgeons to implant the Permaloc electrodes. The procedures discussed in this article involve dissecting the phrenoesophageal ligament, which can create a path for pressurized carbon dioxide to

pass from the abdomen into the mediastinum. Similarly, the insertion of the Permaloc electrode can create a potential track for pressurized carbon dioxide from the abdomen to enter the chest.

Pneumonia & Pulmonary Infections –NSCISC Annual Report, 2018

The National Spinal Cord Injury Statistical Center (NSCISC) at University of Alabama, Birmingham (UAB) supervises and directs the collection, management, and analysis of the world's largest spinal cord injury database. The Center is at the hub of a network of 14 federally sponsored regional Spinal Cord Injury Model Systems located at major medical centers throughout the United States. The NSCISC has developed extensive quality control procedures that further enhance the reliability and validity of the database.

Pneumonia – Jaja, 2019

The authors examined acute spinal cord injury (SCI) patients from two comprehensive databases. This prospective study reported high rates of pneumonia in acute SCI patients and concluded there is a relationship between pneumonia, wound infection, and sepsis occurring during acute admission and poorer functional outcomes following SCI.

Aspiration – Ihalainen,2017

Dysphasia commonly occurs in cervically injured SCI patients. Dysphagia is a contributor to poor outcomes, such as pneumonia and other respiratory complications as well as malnutrition, dehydration, and reduced quality of life. The authors observed a high percentage of traumatic cervical spinal cord injury patients experienced aspiration.

Operative Mortality – Johnson, 2007

The authors utilized National Department of Veteran Affairs datasets to select patients with SCI and subsequent surgical conditions. Their findings revealed the operative mortality rates ranged from 2% to 7%.

Perioperative Complications – Stein, 2014

The authors reported a low prevalence of in-hospital deep venous thrombosis (DVT), pulmonary embolism (PE), and venous thromboembolism (PE and/or DVT) following laparoscopic cholecystectomy. This procedure is very similar to the laparoscopic approach for Permaloc electrode placement.

Wound Infections – Kagawa, 2019

Minimally invasive laparoscopic techniques, similar to those used for Permaloc electrode placement, coupled with improved post-operative care continue to reduce the rate of surgical site infections.

Catheter/Wire Complications – Saval, 2010

This article reports on a retrospective chart review of 57 individuals (SCI and non-SCI patients) requiring an intrathecal baclofen pump. With respect to complications, the authors reported a complication prevalence of 16% over 3 years.

A measure of "durability" of the NeuRx DPS® to stimulate the diaphragm at levels that would produce the indicated endpoint of at least 4 continuous hours of stimulation was not specifically recorded for the primary cohort. Prior to human clinical studies, Peterson et al. (1994) looked specifically at long term use and impedance of the electrodes in an animal model. Peterson (1994) Safety: showed that all electrodes were below 1KΩ impedance in animals implanted up to six months. Note: that impedance was reported in the original HDE submission as 615 ± 92Ω and as stable over time. Also, impedance is measured with each stimulated "breath" and alarms if the device measures an impedance over 2.4KΩ. Thus, there is no evidence of electrode impedance changes over time that would affect the treatment.

Onders reported that 88% (81/92) achieved 4 consecutive hours of pacing, that 76% (70/92) of patients used the NeuRx DPS® for at least 12 hours per day and 60.8% (56/92) of patients achieved 24 hours of device use per day.

Onders, et.al., submitted a further analysis of all patients using DPS 24 hours a day for a minimum of 48 months as of 2020. A total of 17 patients were identified. Range of continuous DPS use was 48 months to 203 months with an average of 150 months. Conclusion is that DP has long term continuous durability.

Assessment of most common device-related adverse events in the NeuRx DPS® population, compared to a similar patient population without DPS use:

The most common occurrence of device-related adverse event in the study was a result of air tracking into the pleural cavity from the CO2 used to inflate the abdomen during surgery, e.g., a capnothorax. One patient experienced a capnothorax that was determined to be serious. Patient 4 sustained a capnothorax during implantation that required an extended hospitalization. In most of the cases, the capnothorax which is just the CO2 from the laparoscopic surgery is rapidly absorbed by the body and quickly resolves after the laparoscopic part of the surgical procedure. One infection occurred local to the in-line connectors in patient 3, which was subsequently externalized and treated with antibiotics. Other incidents of aspiration (3) and upper airway obstruction during sleep (3) occurred and

they were reminded to use a Passy-Muir valve on their tracheotomy during eating and sleep to eliminate that risk.

The largest, and one of the best, databases for spinal cord injured patients is maintained by the National Spinal Cord Injury Statistical Center in Birmingham, Alabama and can be accessed through www.spinalcord.uab.edu. The number one cause of death in this database for all spinal cord injured patients is diseases of the respiratory system (22% of deaths) with pneumonia accounting for 71% of these. In the experience of high tetraplegics implanted with the NeuRx DPS® there were no respiratory deaths.

A review of surgery in patients with spinal cord injury can also be compared to diaphragm pacing surgery. The large Department of Veterans Affairs computer dataset was analyzed for spinal cord injured patients who underwent surgery (ranging from aneurysm repair to appendectomy) and found operative mortality rates ranging from 2% to 7%. There were no peri-operative deaths in the IDE Pivotal trial. The reported complication rate in the VA dataset ranged from 23% (for appendectomy) to 57% (for aneurysm repair). In the IDE Pivotal Trial, none of the commonly tracked peri-operative complications, including venous thrombosis, pulmonary embolus, wound infections, and pulmonary infections were reported. The most common peri-operative adverse event was a capnothorax, which is a common side-effect of laparoscopic surgery, was tracked and involved 21 out of 54 patients (39%).

One report (Chiodo, 2007) of the use of intrathecal baclofen pumps for spasticity showed that 5 out of 44 patients (11.4%) had catheter complications. This is comparable to our reported external wire break rate of 5 out of 48 patients (10.4%). A main difference is that when there is a complication with a Baclofen intrathecal catheter it requires a surgical procedure to correct. The NeuRx DPS® still works even with an isolated broken external wire because of the redundancy of 4 wires implanted. All of the external wire breaks are able to be fixed with an office visit.

Although the surgery is not done in patients with spinal cord injury, placement of a gastric electrical stimulator (Enterra-Medtronic) does involve placement of electrodes in the abdominal cavity either through laparoscopy or open surgery. This allows comparison of adverse events between a transabdominal electrical stimulation procedure and the NeuRx surgical procedure. In one large trial of 55 patients, implanted there was one immediate peri-operative death, in the IDE Pivotal Trial there were no perioperative deaths. In Forster's report, three devices and wires had to be surgically removed for infection while no NeuRx wires needed to be surgically removed for infection. In addition, three patients had surgical revision of the gastric pacemaker while only our first patient in the IDE Pivotal Trial had to have additional wires placed to obtain successful diaphragm recruitment. Since that initial change in mapping technique, no DPS patients required revision surgery.

All-cause mortality in the NeuRx DPS® population, compared to a similar patient population without DPS use:

The graphics below display overall survival (that is, freedom from all-cause mortality) in Kaplan Meier format for both time since injury ("SCI survival," Figure A.2) and time since DPS implant ("DPS survival," Figure A.3). Data displayed are for the primary analysis cohort, that is, the IDE Pivotal Study.

The results indicate a majority of patients surviving at least 22 years, measured from time of injury and at least 19 years after their DPS implant (with a median time between injury and DPS implant of 28.3 months). This compares numerically (without formal hypothesis testing) to values published by the National Spinal Cord Injury Statistical Center, which reported survival among a ventilator-dependent population as 11.2 years for 20-year-olds down to 3.7 years for 60-year-olds (NSCISC Annual Report 2018, Table 14A). Even using the more conservative NSCISC data for those surviving at least one-year post-injury, the relevant numbers are 18.7 years for 20-year-olds, 13.3 years for 40-year-olds, and 7.9 years for 60-year-olds as referenced on Figure A.2.

The results below, therefore, indicate that patients treated with DPS had survival rates that were comparable or better to those reported in the literature in a non-DPS population (NSCISC Annual Report 2018, Table 14A).

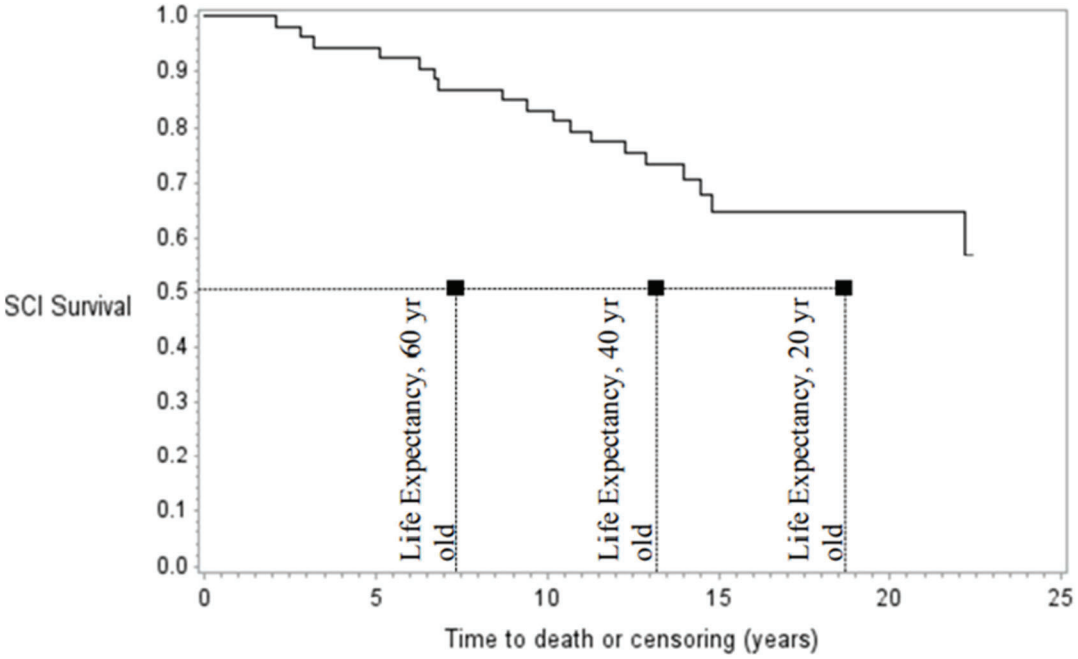


Figure A.2: SCI Survival (years since injury)

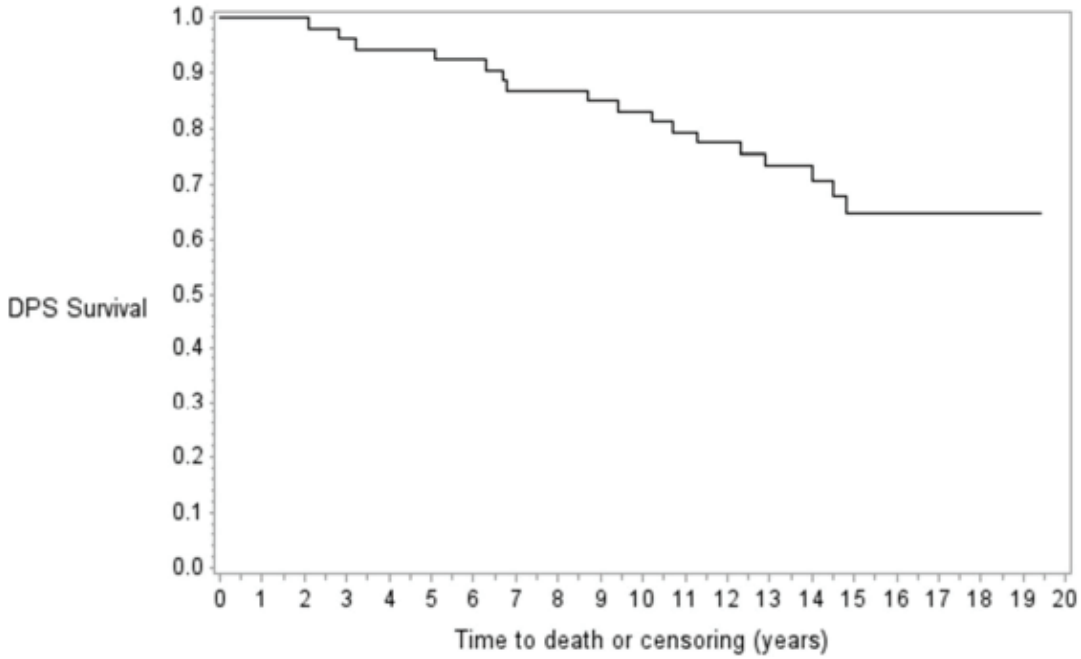


Figure A.3: DPS Survival (years since implant)

2. Effectiveness Results

Efficacy Analysis of the Primary Cohort

For analyses of the Primary analysis cohort, an exact two-sided 95% confidence interval was constructed for the proportion p of subjects meeting the primary endpoint, and the resulting lower confidence bound compared to the PG. This estimate has been summarized with its corresponding 95% confidence interval and compared to a performance goal (PG) representing meaningful clinical benefit.

Primary Endpoint – DPS Use

The primary endpoint was defined as use of the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. This endpoint is reported as the proportion of subjects achieving the endpoint and assessed using binomial methods for the primary analysis.

For this purpose, the Avery diaphragm pacer (PMA P860026) reported a 45% success rate, where “success” was defined as “consistent, adequate ventilatory support from diaphragm pacing for some part of a day.” To provide reasonable assurance of meaningful clinical benefit from the NeuRx DPS®, the PG is defined as the reported Avery success rate for a PG of 45%; meeting the accompanying hypothesis test then constitutes statistical evidence that the success rate with the NeuRx DPS® is greater than the 45% reported by Avery.

The primary analysis cohort is defined to be data collected from the IDE Pivotal Study, for which 96.2% (51/53) of subjects achieved at least 4 continuous hours daily use (Table A.18). The primary endpoint was met on the primary analysis cohort with p<0.001.

Table A.18: Primary Endpoint, Primary Analysis Cohort (n=53)

Event	% (n/N)	95% confidence interval	p-value*
Primary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day)	96.2% (51/53)	(87.0%, 99.5%)	<0.001

* Exact two-sided binomial test against performance goal of 35% (0.35)

Thus, the primary endpoint was met on the primary analysis cohort with p<0.001.

The second test of the primary endpoint is then specified to be based on the pooled IDE Pivotal Study and secondary cohort data (n=106 total). Results are summarized in Table A.19. Thus, the primary endpoint was met on the secondary (pooled IDE Pivotal Study and Onders) analysis cohort with p<0.001.

Table A.19: Primary Endpoint, Secondary Analysis Cohort (n=106)

Event	% (n/N)	95% confidence interval	p-value*
Primary endpoint (proportion of subjects using the NeuRx DPS® to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day)	89.6% (95/106)	(82.2%, 94.7%)	<0.001

* Exact two-sided binomial test against performance goal of 35% (0.35).

Thus, the primary endpoint was met on the secondary (pooled Primary and Secondary cohorts) analysis cohort with p<0.001.

The third and final test of the primary endpoint is then specified to be based on all available sources (n=196 across five studies including the ones cited above), using meta-analytic methods. The results, summarized in Figure A.4, indicate each of the individual studies reaching the 35% performance goal based on exact binomial inference (although this was not a requirement of the success criterion definition) and furthermore that the meta-analytic summary showing success of 92.2% with a two-sided 95% confidence interval of (82.6%, 96.7%), p<0.001 versus the performance goal. The heterogeneity between studies is moderate, with I^2=0.64 indicating some differences between studies in the primary endpoint. The random-effects model used for the meta-analysis incorporates this disparity and appropriately weights the study results, resulting in a lower confidence bound of 82.6% which is less than that derived from pure pooling (95% two-sided lower bound of 85.9% on

178/196 successes). Based on these considerations, the endpoint is met under this analysis as well.

The Primary Effectiveness Endpoint was easily met in the original IDE cohort and in subsequent reported analyzed cohorts.

Meta-Analysis of all Cohorts

The third and final test of the primary endpoint was based on all available sources using meta-analytic methods as stated in the Statistical Analysis Plan. There was a combined n=206 in the five studies, however, 7 patients were not implanted, and 3 patients did not undergo pacing initiation in two of the tertiary sources. Therefore, 10 patients are excluded from this analytic cohort where n=196. The results, summarized in Figure A.4, indicate each of the individual studies reaching the 45% performance goal based on exact binomial inference (although this was not a requirement of the success criterion definition) and, furthermore, that the meta-analytic summary showing success of 92.2% with a two-sided 95% confidence interval of (82.6%, 96.7%), p<0.001 versus the performance goal. In Figure A.4, the data presented for Onders is the data analyzed for only the Secondary cohort of HDE patients where n=53.

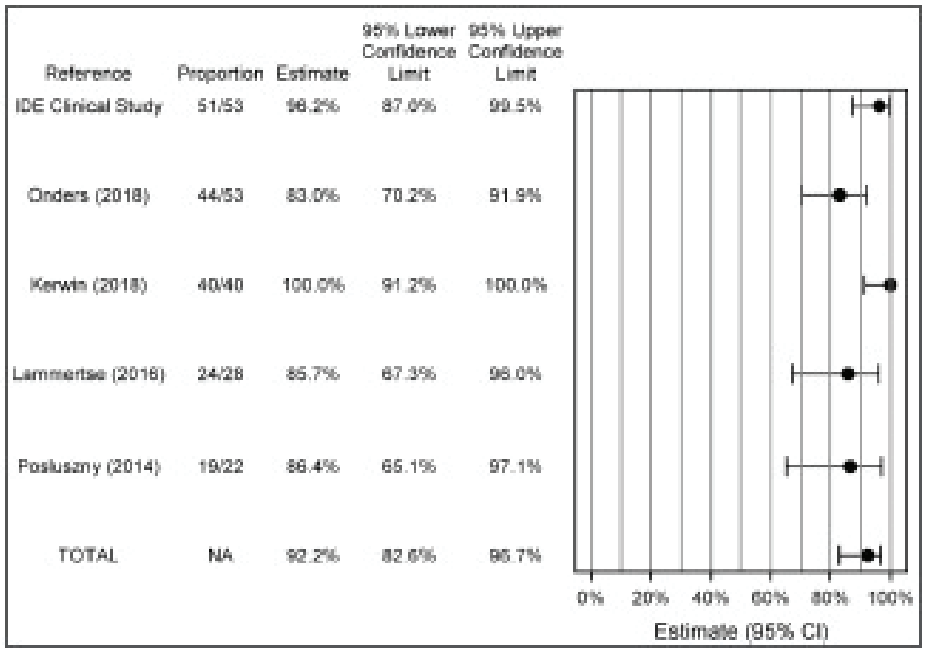


Figure A.4: Forest Plot of NeuRx Success

The heterogeneity between studies was moderate, with I^2=0.64 indicating some differences between studies in the primary endpoint. The random-effects model used for the meta-analysis incorporates this disparity and appropriately weights the study results, resulting in a lower confidence bound of 82.6% which is less than that derived from pure pooling (95% two-sided lower bound of 85.9% on 178/196 successes).

Thus, the endpoint was met under this analysis as well.

For the third cohort, four studies among the five cited in this report provided data on 24-hour use (n=156 across four studies including the ones cited above). The meta-analytic summary (Figure A.5) shows success on 24-hour use of 52.7% with a two-sided 95% confidence interval of (36.2%, 68.6%).

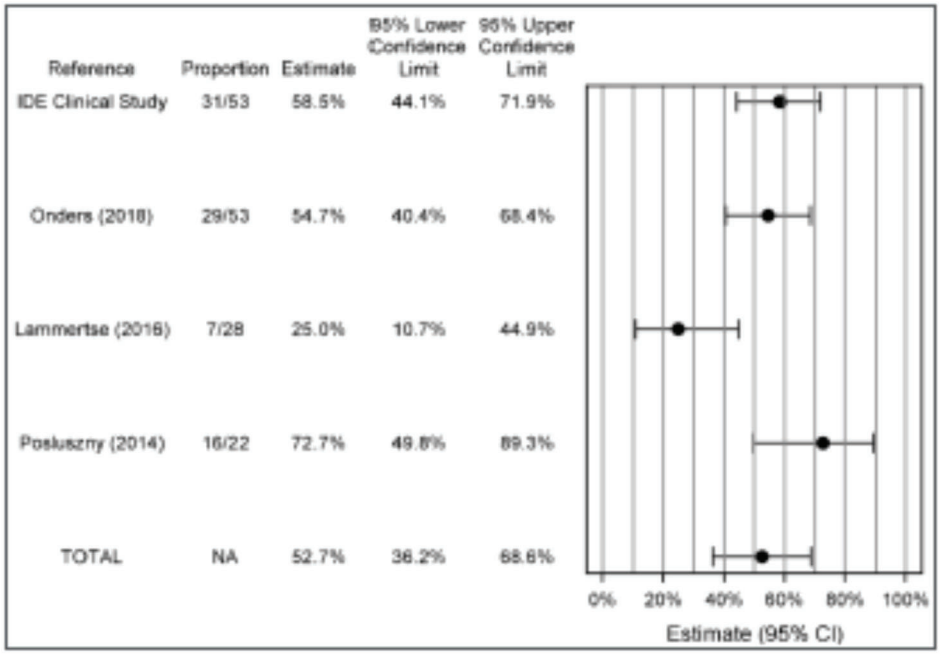


Figure A.5: Forest Plot All Cohorts – Secondary Endpoint (24 hr/daily use)

3. Subgroup Analyses

The following preoperative characteristics e.g., sex/gender, site, age were evaluated for potential association with outcomes and are consistent with national statistics available in 2020 Annual Statistical Report for the National Spinal Cord Injury Statistical Center, University of Alabama at Birmingham, which lists the most common age at injury as 19 years. Their data shows that nearly a quarter (23.7%) of all injuries occurred between the ages of 17 and 22 years, nearly half (47.0%) of all injuries occurred between the ages of 16 and 30, and 12.2% of all injuries occurred at age 60 or older.

Overall, 80.3% of all reported SCIs occurred among males. There was very little variability among Systems with regard to the composition of the participant populations by sex. Among Systems, the proportion of male participants ranged from a low of 70.2% to a high of 86.8%.

Table A.20: pre-operative characteristics, primary cohort

Characteristic	Mean ± SD (N) [Median] (IQR) or % (n/N)
Age at implant	36.1 ± 16.9 (52) [28.4] (22.6,50.5)
Gender Female Male	 22.6% (12/53) 77.4% (41/53)
Age at injury	30.6 ± 18.6 (52) [23.2] (17.9,43.6)
Time from injury (months)	65.1 ± 81.0 (53) [28.3] (12.1,83.3)

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