https://cosmiic.org

Example - Early Feasibility Investigational Device Exemption

IDE Section:

Prior Clinical Studies

4. Prior Clinical Studies

This section contains:

4.1. Background

Three generations of implanted neuroprosthetic systems have been developed in our laboratories at the Cleveland FES Center since the 1980's. Findings from these studies – patient functional outcomes as well as device safety – are briefly summarized below.

A first generation implanted neuroprosthesis (Freehand) was developed in our laboratories (G890084), was successfully transferred to industry (NeuroControl Corp., Valley View, Ohio), was FDA approved (P950035), and was implemented clinically in over 200 patients, with over 40 sites trained in the Freehand surgery. Users were able to obtain greater strength of grasp, increase grasp range of motion, improve ability to manipulate objects and improve performance in activities of daily living. These clinical successes are an indication of the impact of this technology on the lives of individuals with limited function due to spinal cord injuries.

NeuroControl decided in 2001 to exit the spinal cord injury market and enter the larger stroke market, later going out of business, and therefore the Freehand System is no longer commercially available. To date, no other implanted neuroprosthetic hand system or lower extremity trunk stability system has been developed and deployed commercially. Our subsequent development efforts at the Cleveland FES Center have resulted in clinical investigation of two second-generation investigational systems (IST-10, IST-12) that not only brought advancements in design and manufacturability, but also provided greater utility to users. These systems were not commercialized. However, from these experiences, our third-generation system, the NNP, has been developed, and our intention is to bring this system through to eventual commercial deployment.

Investigational versions of these technologies were also developed for lower extremity applications, resulting in systems that are demonstrated to provide standing, stepping, trunk stability, improved reach distance, expanded workspace volume, and improved tissue health (the following IDE's can be referenced: G900108, G040214, G110018). For the purposes of this summary, we are focused on lower extremity applications that involve trunk control only.

4.2. Relevance Of Prior Investigations To NNP-UE Configuration

All neuroprosthetic systems that have been developed in our laboratories over the past 30 years have been based around permanently implanted components. The NNP-UE Configuration is intended to be functionally nearly equivalent to previous upper extremity implanted neuroprosthetic systems, and thus significant published and unpublished pre-clinical and clinical information exists that is highly relevant to this study. Of particular importance, the stimulating and recording electrodes utilized in the NNP System are identical in every aspect to the electrodes that have been utilized with our existing implanted systems, with the exception of the connector design.

We have employed both surface and percutaneous systems over that time period [Peckham, et al., 1980a, Peckham et al., 1980b, Keith et al., 1989, Peckham, et al., 1992, Kilgore, et al., 1997], but we have concluded that implantable systems are required if neuroprostheses are to provide practical function for the lifetime of the user. Although we believe that both surface and percutaneous systems have potential application in muscle conditioning and in short-term research and clinical applications, it has been our clinical experience, and the experience of many others, that surface simulation systems have a high rejection rate by

patients in functional use, and that the maintenance associated with percutaneous systems is prohibitive for long-term clinical use [Handa 1997; Prochazka et al., 1997; Chae et al., 1998; Popovic et al., 1999; Snoek et al., 2000; Alon et al., 2003].

The Networked Neuroprosthesis System in its Upper Extremity configuration (NNP-UE) is functionally nearly equivalent to previous upper extremity implanted neuroprosthetic systems developed at the Cleveland FES Center, with key differences noted in Table 4-1, below. We believe the clinical experience gained to date on these earlier generations of device is directly applicable to the NNP in terms of expected outcomes of subjects for both safety and performance.

TABLE 4-1: COMPARISON OF CWRU-DEVELOPED NEUROPROSTHESES FOR UPPER EXTREMITY

	Generation 1	**Generation 2**		**Generation 3**
	IRS-8 Freehand®	**IST-10**	**IST-12**	**NNP**
FDA applications	G890084 P950035	G950116	G950116	(This application)
Scope of Deployment				
Approx. Era of Use	1986 – 2001	1996-2001	2003-present	
# Subjects implanted	28 (~220)[1]	5	13	
Longest Follow-up	24 years	14 years	7 years	
# IPGs implanted	31	6	19	
# Electrodes implanted	236	40	250	
# Stimulation channels	8	10	14	Configurable
User control method	Shoulder motion	Shoulder or wrist motion	Shoulder, wrist motion, or EMG	Configurable joint motion and EMG
# Myoelectric channels	0	0	2	Configurable
# Joint angle channels	0	2	0	Configurable
Compatible electrodes				
Epimysial-Stimulating	YES	YES	YES	YES
Epimysial-Recording	No	No	YES	YES
Intramuscular-Stim.	YES	YES	YES	YES
Intramuscular-Rec.	No	No	YES	YES
Spiral Nerve Cuff	No	No	YES	YES (not incl. in IDE)
Power	Inductive, through the skin	Inductive, through the skin	Inductive, through the skin	Implanted rechargeable Li-ion batteries

[1] Approximately 220 patients were implanted worldwide as part of the Freehand trial and subsequent commercialization.

4.3. Summary Of Clinical Use Of Electrical Stimulation

Implantable neurostimulation and neuromodulation devices have been utilized since the 1970s. These systems typically utilize relatively similar electrode designs, sizes and a comparable range of stimulation parameters. The maximum stimulation output for a number of commercial neurostimulation and neuromodulation devices are shown in Table 1, along with the maximum stimulus output ranges for systems that have been utilized by the Cleveland FESC over the past 40 years. The maximum charge per phase and charge density per phase are also shown for these devices. The NNP System utilizes stimulation parameters that are at or below the parameters commonly used in commercial devices, as noted in red. Note that the NNP uses electrodes that are identical to FES Center Percutaneous, FES Center Epimyseal, and FES Center Intramuscular electrodes.

TABLE 4 – 2. COMPARISON OF MAXIMUM STIMULATION OUTPUT RANGES FOR TECHNOLOGIES USED CLINICALLY (RED = THIS IDE)

Type of System	Brand	Electrode	510(k), PMA, or IDE #	Max Current (mA)	Max Pulse Width (uS)	Charge/Phase (uC)	Contact Shape	Elec. Diameter	Elec. Length	Surf. Area (mm^2)	Charge Dens per Phase (uC/mm^2/phase)
Motor NP	FES Center	Spiral cuff		2	255	0.5	Disk	1.2		1.82	**28.0**
Motor NP	FES Center	Percutaneous	G890084, G900108, G950116, G040214	20	200	4.0	Cylinder		10.0	10.00	**40.0**
Vagal NS	VNS - Cyberonics	Helix cuff		3.5	1000	3.5	Rectangle	2.0	1.0	6.28	**55.7**
Motor NP	FES Center	Epimyseal	G890084, G900108, G950116, G040214, **P950035**	20	255	5.1	Disk	3.3		8.55	**59.7**
Motor NP	FES Center	Intramuscular	G890084, G900108, G950116, G040214, **P950035**	20	255	5.1	Cylinder	1.3	2.0	7.91	**64.5**
Spinal Cord S.	Precision - Boston Sci	Linear		12.7	1000	12.7	Cylinder	1.3	3.0	12.25	**103.7**
Spinal Cord S.	Genesis-St. Jude	Linear		25.5	507	12.9	Cylinder	1.2	3.0	11.30	**114.4**
Deep Brain S.	Activa - Medtronic	Linear		25.5	450	11.5	Cylinder	1.3	1.5	5.98	**191.8**

4.4. Summary Of Experience with Previous FES Generations

We report on seven clinical evaluations below:

- Freehand System Clinical Trial to Support FDA Approval (P950035)
- Second Generation (IST-10, IST-12) Clinical Experience (1996 – 2003)
- Clinical Results of the IST-10+IJAT System
- Clinical Results of the IST-12+MES System
- Clinical Feasibility Study of the IST System for C5/C6 Hand/Arm Control
- Clinical Feasibility Study of the IST System for C5/C6 Arm and Trunk Control
- Clinical Study of the IRS-8 and IST Systems for lower extremity applications

Our past clinical experience with multiple generations of implantable neurostimulation systems for restoring hand function and trunk stability has allowed us to fully characterize patient outcomes from the standpoint of both safety and effectiveness, as summarized briefly in Table 4-2.

TABLE 4-3. CUMULATIVE CLINICAL EXPERIENCE

SAFETY OUTCOMES		
EVENT	**NUMBER OR RATE**	**COMMENTS**
Death	0 cases	
Serious surgical complication	0 cases	
Infection – Post-Op	0 cases	
Infection – Late	Leads: 1.9% (13/662) Pulse generator: 4.6% (3/65)	In all cases, the infected component was removed and the infection resolved without further incident.
Erosion, tissue breakdown	Erosion: 0 cases; 3 cases of precautionary revision surgery.	Precautionary surgery: 2 cases - implant stimulator surgically repositioned as a precaution against possible erosion. 1 case - one lead surgically repositioned as a precaution.
Electrode lead failure	2.26% (15/662) for both UE and LE applications	Upper Extremity: Kaplan-Meier survival analysis of the electrodes predicts a survival rate of 98.9% +/- 0.9% at 20 years. Lower Extremity: includes 10 electrode failures for locations in posterior thigh, not subject of this IDE.
Connector failure	1.2% (7/564) for in-line connectors	In-line connectors are not subject of this IDE
Device rotation, migration	2 cases	In our first generation device there were two cases of device rotation in the body requiring surgical revision. These devices were not sutured in place. All devices are now sutured in place, and there have been no further incidents of device rotation.
Component removal, or revision as precaution or for medical reasons	1 – lead relocated 5 – electrodes removed (1 subject)	One subject had episode of cellulitis in dorsal forearm, of unknown origin. As precaution, 5 dorsal electrodes were removed.
Component revision for improved performance	2/38 myoelectric recording electrodes	Moved to obtain better signal.

Overheating	0 cases	Earlier systems did not have implanted batteries, but did require the continuous transfer of energy through the skin to the implanted device.
Tissue damage from chronic electrical stimulation	0 cases	As observed in subjects undergoing an upgrade or replacement of an implant or electrode, components are encapsulated with a ~1mm thick connective tissue with no other signs of adverse reaction. The components, when removed, show no signs of corrosion or other degradation.
Device rejection due to materials incompatibility	0 cases	
Electrical shock / leakage currents with external components	0 cases	
Fibrosis, scarring	0 cases (see comment)	No incidents of loss of electrode function (either stimulating or recording) due to excessive scarring
Hermeticity breach	0 cases	
Header fracture	3 cases	All known cases were in subjects using a lower-extremity system for standing. The fractures occurred during extreme activities.
Erratic system performance due to EM sources	More than one documented case.	Subjects with two IST systems implanted in the chest ~20 cm apart experienced degraded performance. The coils were adjusted to operate at different frequencies and the issue resolved in each case. There have been no cases of multiple subjects in the same room creating interference with each other. There have been no cases of wheelchair interference with an implanted system. There have been no cases of erratic system performance in the presence of known EM sources.
FUNCTIONAL OUTCOMES		
Ability to create functional hand grasp patterns	100% (62/62)	
Ability to generate usable control signals (EMG or joint angle)	100% (62/62)	
Improvement in functional use of the hand: Grasp and Release Test	98.4% (61/62)	
Improvement in functional use of the hand: Activities of Daily Living	100% (61/61)	
Regular home use of the hand grasp system	At least 90% at 4-years	First implanted subject used system daily for 24 years. More than 90% of the participants were satisfied with the neuroprosthesis, and most used it regularly. Usage patterns were maintained at least four years post implant.
Increase in reach distance with trunk stimulation	100% (4/4)	
Increase in work volume with trunk stimulation	50% (2/4)	

4.4.1. Freehand System Clinical Trial to Support FDA Approval (P950035)

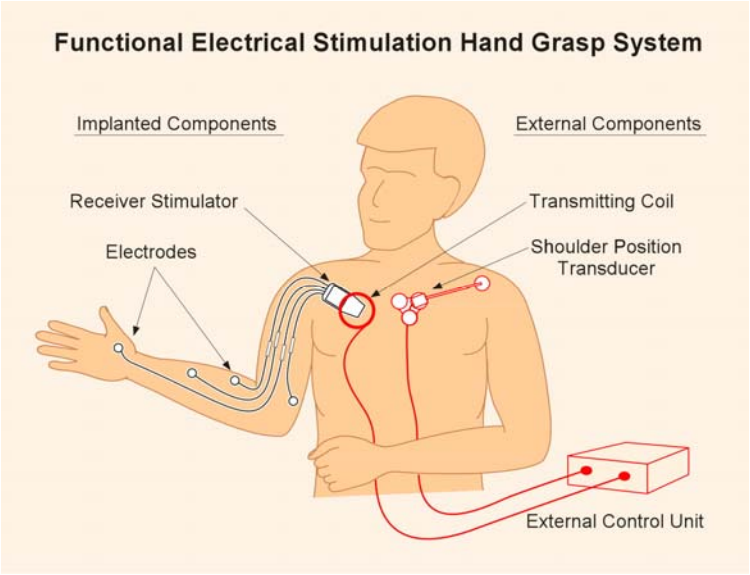

Figure 4-1. Freehand neuroprosthesis. An implanted stimulator provides activation of eight muscles. The system is powered through a coil taped to the user's chest. Control of grasp opening and closing is obtained through movement of the opposite shoulder.

A first generation upper extremity neuroprosthesis for control of hand grasp/release was developed by the Cleveland FES Center and was first implemented in a human volunteer in 1986 [Smith et al., 1987, Keith et al., 1989]. This system is known as the Freehand ® System, and is shown in Figure 4-1. The Freehand neuroprosthesis used an eight-channel receiver-stimulator (IRS-8), eight epimysial or intramuscular electrodes, leads, and connectors. Electrodes are surgically placed on or in the paralyzed muscles of the forearm and hand, and a radio frequency (RF) inductive link provides the communication and power to the implanted receiver-stimulator. The external components of the neuroprosthesis are an external control unit, a transmitting coil and an external shoulder position transducer [Buckett et al., 1988]. The external control unit performs the signal processing of the control inputs and generates the output signal (modulated RF) delivered to the implanted receiver-stimulator. The radio frequency transmitting coil is taped to the individual's chest directly over the implant receiver-stimulator in order to make the inductive powering and communication link. Two grasp patterns are provided for functional activities: lateral pinch and palmar prehension [Peckham et al., 1983, Kilgore et al., 1989]. The lateral pinch is used for holding small utensils such as a fork, spoon or pencil. Palmar prehension is used for acquiring large objects, such as a glass.

To operate the neuroprosthesis, the user depresses a switch on their chest that activates the system, and the user's hand opens into full extension in the lateral pinch mode. Graded elevation of the user's contralateral shoulder results in graded grasp closure [Johnson and Peckham, 1990]. A quick movement of the shoulder "locks" the hand so that it remains closed at the desired degree of closure, until another quick movement of the shoulder

releases the lock command. Depressing the chest switch briefly causes the system to switch to the palmar grasp. Depressing the switch for a longer time turns the system off.

A standard implementation procedure was developed to enable the transfer of the neuroprosthesis into multiple health care institutions and ensure consistent protocols across patients and across institutions. The stages of the implementation procedure were: 1) pre-surgical muscle conditioning using surface stimulation, 2) surgical implantation of the stimulator, placement of stimulating electrodes and augmentative hand surgeries, 3) post-operative stabilization (casting), 4) muscle conditioning, 5) rehabilitation training using the neuroprosthesis, and 6) functional evaluations [Keith et al., 1996; Kilgore et al., 1997].

A multi-center clinical trial was performed to assess safety, effectiveness, and clinical utility of the Freehand neuroprosthesis in persons with spinal cord injury at the C5 or C6 level. This study was initiated by our Center in Cleveland in 1992 under IDE G890084 and was transferred to NeuroControl Corporation in 1994. Pre-market approval (PMA) was obtained by NeuroControl Corporation from the FDA in August, 1997 (P950035). The results of the study are summarized below [see also Keith, 1997; Kilgore et al., 1997; Peckham, 2001]. The investigators were awarded the FDA Commissioner's Award in 1998 for this work.

The Freehand neuroprosthesis produced increased pinch force in every recipient, and there was a significant increase in the ability to move objects of different size and weight [Wuolle et al., 1994; Peckham et al., 2001]. The independence provided by the neuroprosthesis was compared to the maximum independence that could be provided by any other means. With the neuroprosthesis, 100% (n = 28) participants improved in independence in at least one task, and 78% were more independent using the neuroprosthesis in at least three tasks tested. All participants preferred to use the neuroprosthesis for at least one task and 96% preferred to use the neuroprosthesis for at least three tasks tested. More than 90% of the participants were satisfied with the neuroprosthesis, and most used it regularly [Wuolle et al., 1999]. Subsequent follow-up surveys have indicated that usage patterns were maintained at least four years post implant.

In summary, a first generation implanted neuroprosthesis (Freehand) was developed in our laboratories, was successfully transferred to industry (NeuroControl Corp., Valley View, Ohio), and has been implemented clinically in over 200 patients and over 40 sites were trained in the Freehand surgery [Kilgore et al., 1997; Davis et al., 1997; Davis et al., 1998; Carroll et al., 2000; Biering-Sorensen et al., 2000; Fromm et al., 2001; Peckham et al., 2001; Taylor et al., 2002]. Users were able to obtain greater strength of grasp, increase grasp range of motion, improve ability to manipulate objects and improve performance in activities of daily living. This clinical success is an indication of the impact of this technology on the lives of individuals with limited function due to spinal cord injuries. NeuroControl decided in 2001 to exit the spinal cord injury market and enter the larger stroke market and therefore no longer markets the Freehand System [Pancrazio et al., 2006].

4.4.2. Second Generation IST-10 and IST-12 Clinical Experience (1996 – 2003)

A second generation platform technology was developed that allows stimulation of additional channels and control with implanted sensors, referred to as the Implantable Stimulator-Telemeter ("IST") Platform. Clinical implementation of two configurations of the system has been initiated, including a system with 10 stimulus channels with an implanted joint angle sensor, known as the "IST-10" [Peckham et al., 2002], and a system with 12 stimulus channels with two channels of myoelectric signal acquisition [Peckham and Knutson, 2005; Kilgore et al., 2008].

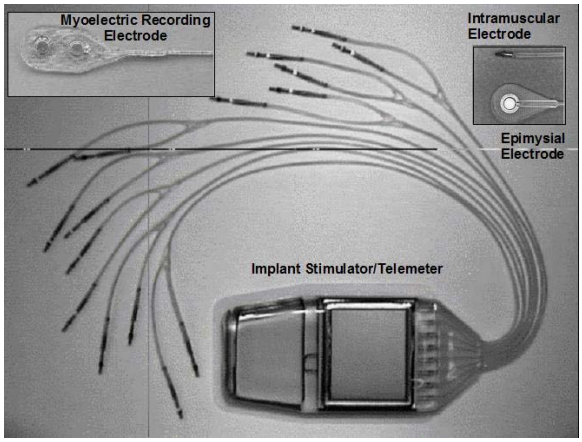

Figure 4-2. Implanted components for the IST-12 system.

The key feature modifications serve to address limitations to the earlier design and enhance functionality and safety, as noted in Table 4-3, below:

TABLE 4-4. KEY DESIGN MODIFICATIONS FOR IST-10, IST-12 SYSTEMS	
External power supply and processing	Allows smaller implanted pulse generator
Bi-directional telemetry	Frees user of all externally donned components except for a single transmitting coil.
10- or 12-stimulation channels	Allows finer control of grasp and improved arm control.
Thick-film micro-electronic circuitry with ASIC	Improved circuit reliability and smaller electronics footprint.
Bipolar feedthrough assemblies	Allows smaller capsule size
Y-branched Leads	Reduction in number of leads and better management of tunneling within the limb.
Implanted joint-angle transducer (IJAT)	Allows 2-degree joint movement transduction with no external components
Myoelectric signal (MES) processor [IST-12]	Allows myoelectric control of grasp. Specialized filtering and stimulus artifact suppression algorithms enhance this function.
Two-level battery charge warnings	Improved safety and usability
Coupling status warnings	
Internal error warnings	

4.4.3. Clinical Results of the IST-10 + IJAT System

Under G950116, five C6 level spinal cord injured individuals were implanted with the IST-10 system and ten electrodes. Four received the implanted joint-angle sensor (the IJAT), and one used an external sensor. The implants were performed in 1996 through 2001. One subject died of causes unrelated to the device after six years of use and another subject died of causes unrelated to the device after eight years of use. This system improves the functional control of their paralyzed limb by giving greater mobility to the proximal limb, more precise and dexterous hand movements, and enhanced control via the implanted sensor. The function provided to these individuals includes both palmar and lateral grasp in all five, elbow extension in four (the fifth has a tendon transfer to provide elbow extension) and forearm pronation/supination in one. All individuals were provided with stimulation of the finger intrinsic muscles that produces better posture of the hand for functional activities. Two of the four individuals were provided with an ulnar-opposition grasp pattern in addition to the lateral and palmar grasp pattern. The ulnar grasp patterns make use of the finger intrinsic muscles to flex the MP joint and extend the IP joints while the thumb is abducted.

The clinical and technological results were very positive. All subjects demonstrated increased grasp strength and range of motion, increased ability to grasp objects, and increased independence in the performance of activities of daily living. All individuals were regular users of the neuroprosthesis. There have been no cases of infection or device rejection. One IST-10 implant failed after two years of operation due to a faulty oscillator. This device was replaced with no further incident, and we have modified our device qualification procedure to screen potential failures of this type. The IJAT, implanted in four of the five subjects, has functioned properly in all subjects. The longest ongoing implant is 13 years. The operation of the electrodes and sensors has been stable over time. This study indicated that advanced neuroprosthetic systems are safe and can provide grasping and reaching ability to individuals with cervical level spinal cord injury.

This study demonstrated the feasibility and desirability of implanting the control transducer in addition to the stimulator and electrodes. However, the installation of the IJAT sensor itself required careful placement of both the magnet and sensor components inside the bones of the wrist and forearm. Although the sensor performed successfully in all subjects, the surgical installation procedure was deemed difficult to perform as a routine clinical procedure that could be easily transferred to other surgeons. As a result, we sought to find sensors that were simpler to install, yet maintained the ability to be implanted in the body. The use of myoelectric signals provided an excellent alternative because the placement of the sensors requires identical skills to the placement of the electrodes, which is already known to be transferable to multiple clinical teams. In addition, the use of myoelectric control is more broadly applicable because the same recording electrode can be used on essentially any active muscle.

4.4.4. Clinical Results of the IST-12 + MES System

Under G950116, preliminary feasibility studies of the use of myoelectric control obtained from externally placed electrodes demonstrated many distinct advantages of myoelectric control for neuroprosthetics [Hart et al, 1998; Knutson et al., 2004]. First, muscles that are too weak to produce the joint motion necessary for the proper operation of the IJAT can still be used to provide MES control. Secondly, the use of MES from the ipsilateral extremity or neck [Scott, et al, 1996], or more distal muscles [Knutson et al., 2004], enables the system to

be implemented bilaterally. Utilizing the IST-12 configuration of the IST Platform, a clinical feasibility study was performed by implanting and evaluating cervical SCI subjects with the myoelectrically controlled IST-12 system. We have implemented the IST System in 13 arms in 10 C5/C6 cervical SCI subjects; in a single arm in each of two C2/C4 cervical SCI subjects; and in one arm in one stroke subject. The results from this study have been extremely positive. This section describes the operation, implementation and results for the clinically deployed IST-12 system.

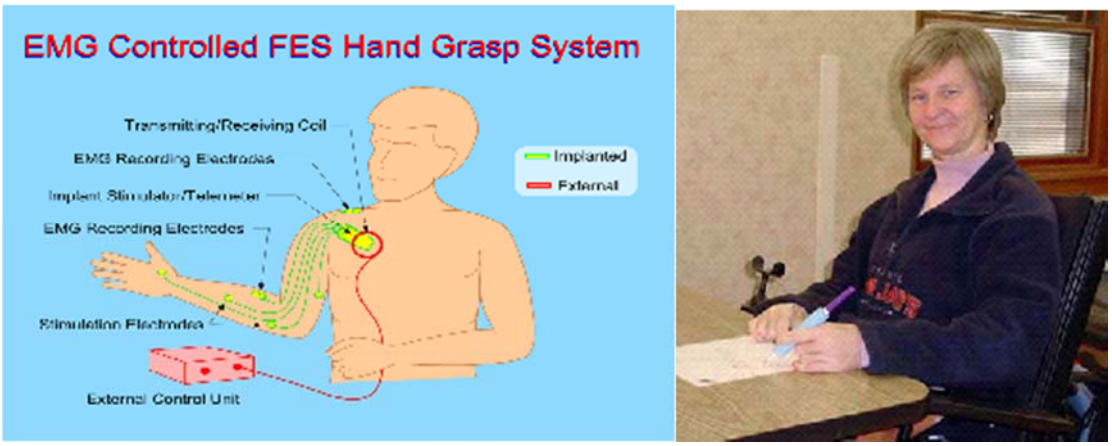

Figure 4-3. Left panel: implementation of the IST as a hand grasp and release neuroprosthesis (not to scale). Right panel: IST recipient using the neuroprosthetic system.

Operation of the IST-12. A diagram of the functional implementation of the IST-12 is shown in Figure 4-3. The control algorithm developed for the IST System uses a common controller template, but can be customized for each user. Typically, generation of two successive high-level bursts of muscle activity in the shoulder or neck are used to turn the system on. The user selects the desired grasp pattern using bursts of activity from the same muscle. Once the pattern is selected, the user has direct proportional control of the degree of hand opening and closing through the myoelectric signal level from their voluntary forearm musculature (either brachioradialis or extensor carpi radialis longus). Strong contraction of this muscle results in hand closing, whereas relaxation of the muscle results in hand opening. If the user desires to hold an object for a long period of time, he/she can initiate a "lock" command, which disengages the grasp stimulation from control by the forearm myoelectric signal. The lock command is initiated by holding the myoelectric signal above a high threshold for two seconds. Once the hand is locked, it will remain locked until an "unlock" command is given. The unlock command can consist of two quick bursts of activity from the forearm (referred to as a "double-click") or a quick burst of activity from the shoulder. The user can also independently activate other functions, such as elbow extension or forearm pronation, by producing a specific pattern of myoelectric activity in the shoulder. The significant advantage of the myoelectric control, in addition to eliminating the need for external switches, is that all control signals are derived ipsilaterally, so the opposite arm is free to be utilized as a helper hand. Therefore, myoelectric control is ideally suited for bilateral implementation.

4.4.5. Clinical Feasibility Study of the IST System for C5/C6 Hand/Arm Control

To date, ten C5/C6 SCI subjects have been implanted with the 12-channel IST device, including three with systems for restoring movement in both hands ("bilateral systems"). All subjects had a cervical level spinal cord injury and were between one to 21 years post-injury at the time of implantation. The results from the first three subjects have been published [Kilgore et al., 2008].

All 10 subjects were able to successfully use the myoelectric signal from their extensor carpi radialis longus (C6) or brachioradialis (C5) for proportional control of grasp opening and closing. In the 13 upper extremities studied (three subjects had bilateral implants), we also demonstrated the ability to generate myoelectric signals from trapezius (N=8), platysma (N=4), deltoid (N=2), and biceps (N=1) muscles. The use of myoelectric control in neuroprostheses allows considerable flexibility in the control algorithms, enabling them to be tailored to each individual subject. The elimination of the need for an externally mounted control source is extremely desirable and makes system use much simpler. The three subjects implemented with bilateral systems have demonstrated the ability to independently control each arm. It should be noted that myoelectric control signals could be obtained *during stimulation* for all 26 recording electrodes (thirteen arms) using a stimulus artifact suppression algorithm. These control signals remained stable throughout the two-year follow-up period.

The study results to date indicate that every subject improved significantly in pinch force strength. In all cases, the pre-surgery pinch force was achieved by passive finger and thumb tone augmented with wrist extension. For most subjects, the pre-surgery pinch force is only useful for acquiring light objects, such as a piece of paper. With the neuroprosthesis turned on, pinch force typically doubled or tripled, and could be used to perform a variety of tasks such as holding a fork for eating or a pen for writing.

Use of the neuroprosthesis allowed every subject to increase the number of objects they could manipulate in the Grasp Release Test, as shown in Table 4-4. Five of the six tasks could be completed by every arm tested using the neuroprosthesis, and all six tasks could be completed by 8/13 arms. In contrast, prior to surgery only one subject could manipulate as many as four objects, and most subjects could only manipulate the two lightest objects.

TABLE 4-5: GRASP AND RELEASE TEST RESULTS IN 10 SUBJECT / 13 ARMS

Grasp Release Test Performance (Maximum Number of Objects = 6)													
	Participant												
	A	BL	BR	CR	CL	D	E	FR	FL	G	H	I	J
Pre-Surgery	0	3	2	3	2	2	2	2	2	2	2	4	3
Post-Surgery, NP Turned OFF	0	4	4	3	2	2	2	2	2	3	2	4	4
Post-Surgery, NP Turned ON	5	6	6	6	6	5	5	6	6	5	5	6	6
Improvement - ON versus OFF	+5	+2	+2	+3	+4	+3	+3	+4	+4	+2	+3	+2	+2

The ability to perform activities of daily living was assessed for 13 arms in ten subjects, as shown in Table 4-5. Every subject demonstrated improvement in at least two activities, with one subject demonstrating improvement in 11/12 activities tested and another subject

demonstrating improvement in 9/9 activities tested. Improvement in these activities generally indicates that the subject can complete the task more independently with the neuroprosthesis than they can when the neuroprosthesis is turned off, although improvements in the quality of performance, ease of performance and time to complete the task are also possible. All thirteen arms in the ten subjects showed improved function in eating with a fork and 12/13 showed improvement in writing with a pen. These tasks have been shown to be some of the most common tasks for which subjects use their neuroprosthesis in the home environment. Subjects with *bilateral systems* are able to perform activities such as using a fork and knife to cut food, using two hands to screw and unscrew a lid on a jar, and brushing hair while blow-drying.

TABLE 4-6: ACTIVITIES OF DAILY LIVING TEST RESULTS IN 10 SUBJECT / 13 ARMS

Activity of Daily Living Performance Changes

("•" = Improved; "-" = Not Improved; " " = Not Tested)

	Participant													
Activity	A	BL	BR	CR	CL	D	E	FR	FL	G	H	I	J	**Number Improved/ Number Tested**
Eating with a Fork	•	•	•	•	•	•	•	•	•	•	•	•	•	13/13
Writing	•	•	•	•	•	•	•	•	•	•	•	•	-	12/13
Drinking from a Glass	•	•	-	•	-	•	-	•	-	•	•	•	•	9/13
Using a Phone		-	-	•	-	-	•	•	•	-	-	•	•	6/12
Brushing Teeth	•	-			-	•	•			•	-	•		5/8
Using a Computer CD					-	-	•	-	•	•	-	•		4/8
Brushing Hair		•	•							•	•			4/4
Drinking from a Mug						•				•	•	•		4/4
Eating with a Spoon						•				•		•		3/3
Eating Finger Foods	•									•				2/2
Applying Chapstick		•	•											2/2
Drinking from a Wine Glass										•			•	2/2
Applying Lip Gloss		•												1/1
Wiping Nose		-	•											1/2
Shaving with Electric Shaver						-	-			•				1/3
Using a USB Drive							-	•						1/2
Removing Wallet from Pouch							•							1/1
Open/Close Drawer													•	1/1
Cutting Food												•		1/1
Using a mobile phone								•						1/1
Moving a Chess Piece									•					1/1
Opening a jar									•					1/1
Eating an Apple									•					1/1
Eating Yogurt									•					1/1
Taking Medicine							-		-					0/2
Eating a Sandwich									-					0/1
Total Tasks Improved	5	6	5	4	2	6	6	6	8	11	5	9	5	

4.4.6. Clinical Feasibility Study of IST System for C5/C6 Arm and Trunk Control

Improved reach and seating posture through electrical activation of muscles that control the shoulder and trunk can provide important functional benefits for individuals with cervical level SCI. In order to explore these benefits, a C5 SCI individual was implemented with dual IST-12 systems, providing a total of 24 channels of stimulation and 4 channels of myoelectric signal recording. The four EMG channels implanted include the trapezius, biceps, deltoids (selected for upper extremity control) and extensor carpi radialis longus (typically used for hand grasp control). Eight of the stimulation channels were used for hand grasp and six were used for trunk stimulation to provide posture control, trunk stability and weight relief. The shoulder and elbow implanted stimulation channels include the suprascapular nerve, the radial nerve, and the pectoralis major (which was transferred to the scapula to replace the function of the denervated serratus anterior), rhomboids and pronator quadratus muscles.

During trunk function testing the subject was asked to perform single plane and single-joint movements under four different conditions: no stimulation, trunk stimulation, shoulder stimulation and trunk plus shoulder stimulation. During trunk stimulation, his six trunk stimulation channels are activated to stabilize his trunk posture and reduce the scoliosis in his back. During shoulder stimulation, fixed average levels of stimulation are constantly provided to three channels: suprascapular nerve cuff (innervating the infraspinatus and supraspinatus), radial nerve cuff (innervating mainly triceps) and pectoralis major (transferred to act as a scapular stabilizer to replace the actions of the denervated serratus anterior). The results show that shoulder stimulation provides an increase in arm elevation angle in the workspace area between the coronal and the scapular elevation planes (~0-30°). For larger planes of elevation (>30°), this difference is not as evident. Stimulation to the suprascapular nerve improves external rotation increasing the overall range of motion for this degree of freedom. Horizontal flexion-extension also improves even though pectoralis major is not utilized. It appears that providing glenohumeral stability (through the stimulated suprascapular nerve) and scapular stability (through the stimulated scapular stabilizer) improves the overall range of horizontal flexion. Further testing is ongoing.

Studies utilizing myoelectrically controlled neuroprostheses show that this feature allows considerable flexibility in the control algorithms that can be utilized. The elimination of the need for an externally mounted control source is extremely desirable and makes the system much simpler to use. Therefore, these features are key design specifications for the NNP-UE System utilized in the proposed study.

4.4.7. Clinical Study of the IRS-8 and IST-12 for Lower Extremity

While trunk and upper extremity FES systems have not previously been studied together, the combination is expected to improve overall functionality of people with SCI by extending their reaching distance and expanding their functional workspace. In addition, early work suggests FES of the postural muscles may improve overall sitting stability, positively impact the mechanics of wheelchair propulsion and improve tissue health. The following investigational results were obtained using the equivalent of the second generation (IST-12) FES system.

The effects of FES on reach distance and three-dimensional workspace were studied in four subjects with motor complete SCI implanted with electrodes placed on the lumbar erector

spinae [Sahana, 2004]. To characterize three-dimensional functional workspace, subjects extended their arms through a sweeping movement as far as possible without losing balance. To characterize forward reach, subjects held objects of varying weights and reached to targets placed in the sagittal plane. Two of four subjects experienced an increase in functional work volume; all four subjects were able to reach a greater distance from their body and hold heavier objects with FES on compared to off.

In a series of six subjects with chronic mid-cervical or thoracic level SCI receiving continuous low-level stimulation to the hip (gluteus maximus, posterior adductor, or hamstrings) and trunk extensor (lumbar erector spinae and/or quadratus lumborum) muscles, stabilization of the pelvis and trunk was found to positively impact the mechanics of manual wheelchair propulsion and reduce both perceived and physical measures of effort [Triolo, 2013].

Postural trunk and hip stimulation has the potential to result in improved pelvic tissue health as measured by transcutaneous oxygen tension. In a convenience sample of seven subjects with an implanted FES system, electrical stimulation of the trunk muscles was applied [Wu, 2013]. Each subject had customized muscle sets; however, all subjects received stimulation bilaterally to the lumbar paraspinal and gluteus maximus muscles. In addition, some subjects had stimulation of the quadratus lumborum and trunk stabilization, with hip extension strengthened by the semimembranonsus and posterior portion of the adductor magnus. For sacral sitters, transcutaneous oxygen tension increased while stimulation was on, and returned to baseline when off.

4.5. Summary of Published Data on Implantable Li-Ion Rechargeable Batteries

Li-ion primary and secondary batteries are very desirable for use in implantable medical devices because of their high energy density. There is now nearly a decade of experience with rechargeable Li-ion batteries and the safety record with these batteries has been excellent. This section presents a brief summary of the available reports, indicating that these batteries have been used in widely distributed commercial devices (spinal cord stimulators) and multiple research feasibility studies.

Li-ion rechargeable batteries are most commonly used in Spinal Cord Stimulators (SCS) when the application requires high power needs. To date, there are no large-scale study reports indicating any specific adverse events related to the Li-ion battery. Commercial SCS devices that utilize a Li-ion rechargeable battery include the Eon Mini (St. Jude Medical - originally ANS), the PrecisionPlus (Boston Scientific – originally Precision, Advanced Bionics), and the RestoreUltra (Medtronic). Their respective PMA's are: P010032, P030017, and P840001. A search of FDA's MAUDE database was conducted to determine the nature of battery-related failures resulting in patient harm, and potential over-heating that may cause patient adverse events. The MAUDE database was searched for records between 2001 - October, 2013, for these three products. A total of 897 reports were identified for all adverse events; only 5 related to battery issues, and all of those were for premature battery depletion of the Medtronic RestoreUltra. There were no reports of adverse events related to components overheating or battery charging issues.

An investigational device that performs cardiac contractility modulation (CCM) is based on a Li-ion rechargeable battery due to the continual power delivered by the CCM device. A multi-center study of this device was reported by Borggrefe et al., [2008]. In the study, 164

patients received Li-ion powered CCM devices. There were no reported adverse events related to the Li-ion battery or to loss of power in the clinical trial.

A small injectable stimulator has been developed called the Bion. One version of the device utilizes a small Li-ion rechargeable battery as the power source. This device was recently studied as an investigational device for treatment of headache pain through stimulation of the occipital nerve [Trentman et al., 2009]. Nine subjects received this device, with no reports of adverse events related to the rechargeable battery. One battery failed to charge and was replaced.

A new cochlear implant has been developed that utilizes an implanted Li-ion battery [Briggs et al., 2008]. In a feasibility study of three subjects, there were no adverse events related to the technology. The Li-ion battery was reported to have functioned well and provided significant power capacity.

In summary, Li-ion rechargeable batteries have now been utilized in a wide variety of clinical applications. They have been utilized in both large and small-scale studies. To date, there are no reports of serious adverse events directly related to the presence of the rechargeable battery.