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Example - Early Feasibility Investigational Device Exemption

IDE Section:

Investigational Plan

Early Feasibility Study of the Networked Neuroprosthesis for Grasp and Trunk Function in Spinal Cord Injury

IDE Number: G14_____

Case Western Reserve University
10900 Euclid Ave.
Cleveland
Ohio 44106

[redacted]

[redacted]

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1. PROTOCOL SYNOPSIS

The table below provides a summary of the Early Feasibility study intended to support the development of the device final configuration and establish appropriate endpoints for a pivotal clinical trial.

Table 1. Clinical Study Protocol Synopsis

Title	Early Feasibility Study of the Networked Neuroprosthesis for Grasp and Trunk Function in Spinal Cord Injury
Device	Networked Neuroprosthesis (NNP): This Early Feasibility Study will explore two different configurations, the NNP-UE (upper extremity) and NNP-T (trunk) Configurations
Intended Use	The NNP is an implantable, configurable neuromodulation platform that provides both activation and inhibition of nervous tissue, and sensing of physiological and environmental signals. • The NNP-UE Configuration activates nerves of the upper extremity (arm and hand), and senses motion and/or EMG in order to provide hand grasp. • The NNP-T Configuration activates nerves of the trunk in order to facilitate reaching and provide trunk stability.
Study Objective	Perform an early feasibility study of the NNP System in configurations that provide both grasp and trunk function to individuals with cervical level SCI, in order to finalize key elements of the device, its clinical implementation, and study design prior to conducting a pivotal clinical trial.
Patient Population	Subjects will have diagnosis of cervical level spinal cord injury, either complete or incomplete, and will be medically cleared for surgery. Subjects will exhibit electrically active musculature to enable development of hand grasp patterns and trunk stability patterns.
Study Design	Prospective, non-randomized, with patients serving as own control (stimulation ON v. OFF)
Patient Timeline	1. Patient screening 2. Pre-operative muscle conditioning with surface stimulation 3. Implant surgery 4. Programming session(s) for exercise 5. Home use for exercise and conditioning 6. Programming session(s) for Grasp and Trunk stimulation, Control and functional evaluation 7. Home use 8. 6-month follow-up
Primary Endpoint *Performance Assessment*	• Hand function: Improvement in Grasp and Release Test, stimulation ON v. OFF at 6 months • Trunk function: Trunk-Stimulated Reaching Ability, stimulation ON v. OFF, at 6 months • Hand and Trunk Combined: We will use the Early Feasibility Study

	to establish an appropriate endpoint that captures the combined performance of both systems.
Primary Endpoint *Safety Assessment*	• Serious Adverse Events (SAEs) at 6 months • Device adverse events at 6 months
Secondary Endpoints	• Active and passive range of motion • Manual Muscle Test • Muscle Excitability • Pinch Strength • Sensation • Seated Posture • Activities of Daily Living (ADL) • Participant Satisfaction Survey • Device Usage Log • All Adverse Events
Primary Hypothesis	NONE – Early Feasibility Study
Statistical Methods	Descriptive statistics only for Early Feasibility Study
Sample Size	Up to 10 subjects will be enrolled.
Study Centers	1 site
Follow-Up	Post-operative, post-muscle conditioning, post-implant at 6-months, and annually thereafter for a minimum of 3 years.
Study Duration	The study duration is expected to last approximately 24 months from the time of first subject to final subject enrollment + 6-month follow-up.

2. GENERAL INFORMATION

2.1. Protocol Title

Early Feasibility Study of the Networked Neuroprosthesis for Grasp and Trunk Function in Spinal Cord Injury

IDE NUMBER: G14_____

2.2. Sponsor

CASE WESTERN RESERVE UNIVERSITY

Primary Investigators:

[redacted]

Clinical Monitor:

[redacted]

3. PURPOSE

The purpose of this study is to perform an early feasibility study of the Networked Neuroprosthesis (NNP) System in configurations that provide both grasp and trunk function to individuals with cervical level SCI, in order to finalize key elements of the device and its clinical implementation prior to designing a pivotal clinical trial.

The specific goals of this early feasibility study include the following:

- Finalize technology design, particularly ergonomically-related design aspects.
- Evaluate and finalize the control algorithms that enable users to easily and intuitively control the functions of the NNP System.
- Finalize the implantation procedure.
- Finalize software features related to system customization with each subject.
- Finalize methods and procedures for most effectively training subjects in the use of the system.
- Establish clinical trial endpoints that are appropriate for a multi-functional system.
- Finalize the follow-up schedule, balancing critical data collection with the practical issues related to the participation of severely paralyzed subjects (e.g., travel considerations, attendant care, etc.).

4. BACKGROUND INFORMATION

Spinal cord injury (SCI) at the cervical level can result in complete paralysis below the level of the lesion (tetraplegia), leading to extensive disability. These individuals are dependent on caregivers for daily activities such as eating, basic hygiene, and respiratory care. Individuals with SCI often sustained their injury in the second or third decade of life and can be expected to live a near normal lifespan with proper medical management [NSCISC, 2007] meaning these individuals often live with their disabilities for 40 or more years. For individuals with mid-cervical level spinal cord injury, restoration of hand function is their top priority [Anderson, 2004]. Conventional methods, typically braces and orthotics such as the wrist-driven flexor hinge-splint, can provide limited grasp function but are often abandoned due to a variety of factors, including poor cosmesis, weak grasp force, and limited adaptability [Allen, 1971]. As an alternative, neuroprostheses provide a promising method for significant gain in hand and arm function for cervical level SCI.

Trunk instability may be one of the primary contributing factors to upper extremity injury and painful chronic health problems after paralysis. Sitting for prolonged periods of time in postures that place the lumbar spine in kyphosis and tilt the pelvis posteriorly can lead to frequent pressure sores, restrict respiratory volumes, and compromise the ability to perform essential transfers or propel a manual wheelchair. Individuals with less trunk control due to higher-level injuries, have a greater propensity to develop rotator cuff disorders [Sinnott, 2000]. Furthermore, lack of trunk control compromises the ability to manipulate objects in the environment by

forcing individuals with SCI to rely exclusively on unimanual reach. For these reasons, trunk stability has been identified as one of the higher priorities for motor system recovery in individuals with SCI [Anderson, 2004; Brown-Triolo, 2002].

Neuroprostheses utilize small electrical currents to activate peripheral motor nerves, resulting in controlled contraction of paralyzed muscles. The fundamental aspects of electrical activation of nerves are well understood and the safe levels of stimulation for long-term use have been established. Muscle contractions can be coordinated to produce grasp opening and closing; thumb opening, closing and positioning; wrist extension/flexion; forearm pronation; elbow extension; shoulder stabilization; and trunk stabilization for cervical level SCI individuals. The individual controls the coordinated muscle activity through movement of their voluntary musculature.

This study will utilize the "Networked Neuroprosthetic" (NNP) System (described more fully below) to provide grasp and trunk stability for cervical level SCI.

5. INTENDED USE

The NNP is an implantable, configurable neuromodulation platform that provides both activation and inhibition of nervous tissue, and sensing of physiological and environmental signals.

- The NNP-UE Configuration activates nerves of the upper extremity (arm and hand), and senses motion and/or EMG in order to provide hand grasp.
- The NNP-T Configuration activates nerves of the trunk in order to facilitate reaching and provide trunk stability.

6. DEVICE DESCRIPTION

The implantable components of the Networked Neuroprosthetic (NNP) System are shown in Figure 1 below, and include **remote sensing modules** that sense EMG signals via **recording electrodes,** the signals from which can be used as inputs for control. **Remote actuator modules** provide stimulation to peripheral nerves via **stimulating electrodes**, and are linked to other networked components by **network cables**. A **power module** provides power to all the networked components, as well as wireless communication to the external programming system.

The external components include the **control tower**, which serves as both a clinical programmer (when used in its clinical configuration) and as the patient's charger (when used in its stand-alone configuration). For clinical programming, communication from the control tower to the power module is achieved with a MedRadio communication link (402–405 MHz). Recharging of the implantable power module is achieved with an external **recharge coil** and an inductive recharge field (3.5kHz) The implanted system can be put into a safe, deactivated mode with an external **reset magnet**.

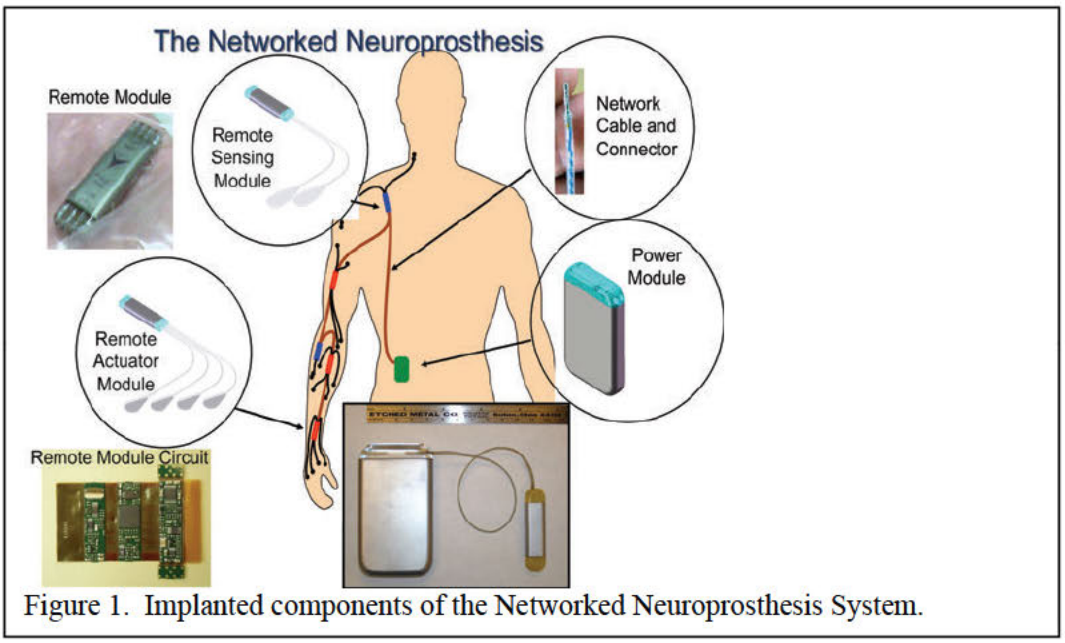

Figure 1. Implanted components of the Networked Neuroprosthesis System.

The NNP System is intended to provide grasp, reach and trunk stability functions to subjects with tetraplegia in order to improve their independence in activities of daily living. After subjects are implanted with the NNP Power Module, Remote Modules, Electrodes, and Connectors, this study will evaluate each subject's ability to make use of voluntary muscle contraction to control the coordinated activation of paralyzed muscles into the functional motions of hand grasp and trunk extension.

The implanted components will be programmed by a technical specialist using the Control Tower, the Programming Computer and Clinical Interface software. The goal is to optimize the subject's performance using the implant as naturally as possible based on their unique presentation based on: voluntary muscle strength, passive and active range of motion, stimulated muscle response, and most importantly, different functional goals and home/community environments. Briefly, there are two major aspects of neuroprosthesis programming:

- **Pattern set-up for grasp and/or trunk stability.** This consists of electrode profiling to characterize thresholds for activation and maximum current for selective activation, followed by creation of a grasp template or trunk extension template which establishes the relative activation of each muscle from 0% to 100%.

- **Control signal setup.** The clinician establishes the logic and proportional control methods used by the subject to perform various tasks, including methods to choose the selection of grasp patterns, open and close the hand proportionally, "lock" and "unlock" the hand, proportionally extend and relax the trunk, and place the system into "sleep" mode or turn off completely.

7. POTENTIAL RISKS & BENEFITS

7.1. Potential Risks

The risk profile is anticipated to be very similar in level of severity and likelihood to the types of adverse events encountered with the NeuroControl Freehand System. As a clinical site for the NeuroControl Freehand, our prior experience with 44 subjects (51 devices), documented the following device-related adverse events:

- Infection
- Electrode lead failure
- Connector failure
- Implant and/or electrode revision surgery
- Implant and/or electrode removal

With regard to potential adverse events, the most serious include but are not limited to the following:

- Loss of life
- Loss of limb, additional paralysis
- Permanent injury or tissue damage leading to functional deficit
- Inpatient hospitalization required to maintain/restore function
- Elective surgical revision with no loss of pre-implant function

Other, less serious, potential adverse events include but are not limited to:

- Chronic pain
- Temporary functional deficit
- Outpatient treatment for infection, burn, or temporary pain

7.2. Mitigation of Risks

The NNP does not present significantly different risks than those presented by earlier generations of this technology. The highest-level risks are primarily related to the surgical procedure and physiological response to the implanted components, particularly infection, tissue erosion and nerve compression.

SUMMARY OF PATIENT RISK MITIGATIONS

SCREENING	Subjects are carefully screened and will be excluded on the basis of health or medical issues that could exacerbate the safety profile of the system.
	The EFS IDE study is limited to fewer than 10 subjects.
INFORMED CONSENT	All subjects will be required to sign an informed consent document outlining the purpose of the study, the methods and procedures used, the risks and benefits of participating, and their rights as a subject.
USER RESTRICTIONS	Based on the results of our current testing, it does not appear necessary to restrict the environment of use for subjects. Nevertheless, training and consent documents will convey the need to potentially do this, based on experience with our first subjects.

USER TRAINING	Training for both subjects and clinical staff will emphasize safe use of the system in accordance with its design and labeling.
	Subjects will be educated through direct training on how to safely use the system, and how to identify certain device-related safety and performance events that should be reported as part of the investigation.
	Training for both subjects and clinical investigators / staff will include review of contraindications, warnings, precautions, and instructions.
SUPERVISED USE	In addition to being trained in how to use the system, subjects in the Early Feasibility IDE study will undergo sessions in which their independent use of the system is supervised by clinical investigators, prior to being discharged to use the system at home.
LABELING	Warnings and precautions are included in the Patient Manual to address concerns about risks posed by the investigational device.
	The section of the Patient Manual entitled, "When to Call Us" identifies key safety issues and events that should be reported to the FES Center investigators as part of the trial.
CLINICAL FOLLOW-UP	Subjects will be followed regularly as part of the clinical study, and every measure will be taken to assure long-term follow-up beyond the defined study duration.

7.3. Potential Benefits

- Subjects may experience improved hand function, potentially giving them greater independence in performing activities of daily living.
- Subjects may experience improved trunk stability during seated reaching and bimanual activities, and/or during wheelchair propulsion.

8. STUDY DESIGN

This is a prospective, non-randomized study that will be conducted at a single investigational center, with subjects acting as their own control.

It is anticipated that as many as 100 patients will be screened to assure that 10 subjects meet the eligibility criteria. The number of subjects to be screened is based on our past experience with this patient population. A small number of subjects screened will fail the inclusion/exclusion criteria, approximately 10-20%. However, a significant number of subjects screened will encounter health problems, such as a prolonged infection or pressure sore, before they are able to proceed to the implantation phase. In addition, subjects experience many other life changes, such as the loss of an attendant or family support, and these events significantly impact their decision regarding whether to proceed with the implantation of the device. These events are due to the severe disability experienced by these patients, resulting in many social and health events that disrupt their participation in the study.

All subjects who meet the established Inclusion/Exclusion Criteria for the study and who provide written informed consent will be enrolled.

8.1. Study Population

8.1.1. Inclusion Criteria

Subjects will be eligible for inclusion in the study if they meet **ALL** of the following Inclusion Criteria:

- Skeletally mature (age > 16 years)
- Diagnosis of cervical level spinal cord injury, either complete or incomplete
- Peripheral nerve innervation to upper extremity and trunk muscles, including a grade 3/5 or higher stimulated strength (Manual Muscle Test) in at least two of the following muscles in one arm: AdP, AbPB, FPL, EPL/EPB, EDC, FDS, FDP, PQ, ECU, ECRB, ECRL, FCU, FCR, 1DI; and in at least two of the following muscles: left/right gluteus maximus, left/right erector spinae, left/right quadratus lumborum, left/right iliopsoas, and left/right latissimus dorsi.
- Biceps/brachialis/brachioradialis strength of 2/5 or higher on Manual Muscle Test
- Able and willing to take part in study
- Medically stable – cleared for surgery

8.1.2. Exclusion Criteria

Subjects will be excluded from the study if **ANY** of the following conditions are present:

- Other neurological conditions (MS, diabetes with peripheral nerve involvement)

- Presence of other active implantable medical devices with unknown or untested interaction with the NNP implant
- Adverse interaction between system components and typical EM sources in subject's home and work environments, including wheelchair or other active implantable devices.
- Active untreated infection such as decubitus ulcer, urinary tract infection, pneumonia
- Extensive upper extremity denervation (fewer than two stimulatable hand muscles and two stimulatable trunk muscles)
- Less than six months post-injury (neuroprosthesis implantation delayed until criteria met)
- Currently pregnant (neuroprosthesis implantation delayed until no longer pregnant)

8.1.3. Study Duration

The duration of the study is expected to last approximately 30 months from the time of first subject to final subject completing the 6-month follow-up evaluation.

8.1.4. Withdrawal from the Study

Subject withdrawal from the study will only be used in extreme circumstances: subjects will be placed in either "active" or "inactive" status, depending on their personal situation. Because SCI subjects experience many life-changing events, we have found that it is detrimental to require withdrawal from the study if a subject is unable to conform to the specific follow-up dates and evaluations. Rather, we have found it is prudent to consider the subject to be considered "inactive". This provides subjects with the opportunity to recover from their life event and return to active involvement in the study without a significant loss of information. In addition, it is of significant benefit to the subject if they continue to exercise using the implanted system even if they do not return to the laboratory for functional evaluations, because exercise maintains muscle strength and tends to limit the development of irreversible contractures.

There is no specific time limitation regarding how long a subject may remain inactive. Inactive subjects are subjects that are experiencing a life event that prevents them from maintaining the standard follow-up schedule. These events could be medical, such as a prolonged pressure sore, or non-medical, such as the loss of a support attendant. The "inactive" status is one in which there is the potential that the subject will return for standard follow-up in the future (such as when the medical condition resolves or when the non-medical situation improves). There is no scientific or clinical advantage to the surgical removal of the implanted system in these cases, and the possible advantage to leaving the system in place is that the subject might be able to return for follow-up and

provide additional study data. Surveillance of inactive subjects will consist in contacting them on a semi-annual basis, at a minimum, to determine if there is a resolution of the medical condition. Subjects will be instructed to contact the investigators in the event of a medical adverse event. Subjects are instructed to consult with their local treating physician for medical events and are instructed to provide the contact information of the investigators to the local treating physician. If subjects fail to respond to repeated attempts at contact, they will be considered lost to follow-up and discontinued from the study.

In the unlikely event that a subject experiences continual health problems or exhibits self-destructive behavior where there is concern that the subject may put themselves at risk, the subject may be withdrawn from study with the recommendation to have the implant removed.

Subjects requesting to have the implant removed will be withdrawn from the study.

9. STUDY PROCEDURE

9.1. Overview

The overall schedule of events for each subject is shown in Figure 2. In summary, eligibility is determined in the screening process before the NNP stimulation system is surgically implanted in the subject's trunk and upper extremity. Trunk and upper extremity components are implanted in one or two surgical sessions and subsequent training and testing activities for both applications will occur concurrently. After a period of healing, the subject begins an exercise regimen to build muscle strength and endurance. Following that, the subject undergoes a period of training, followed by an active evaluation period. The exercise, training, and active evaluation phases last approximately six months, after which the subject is discharged to long-term follow-up.

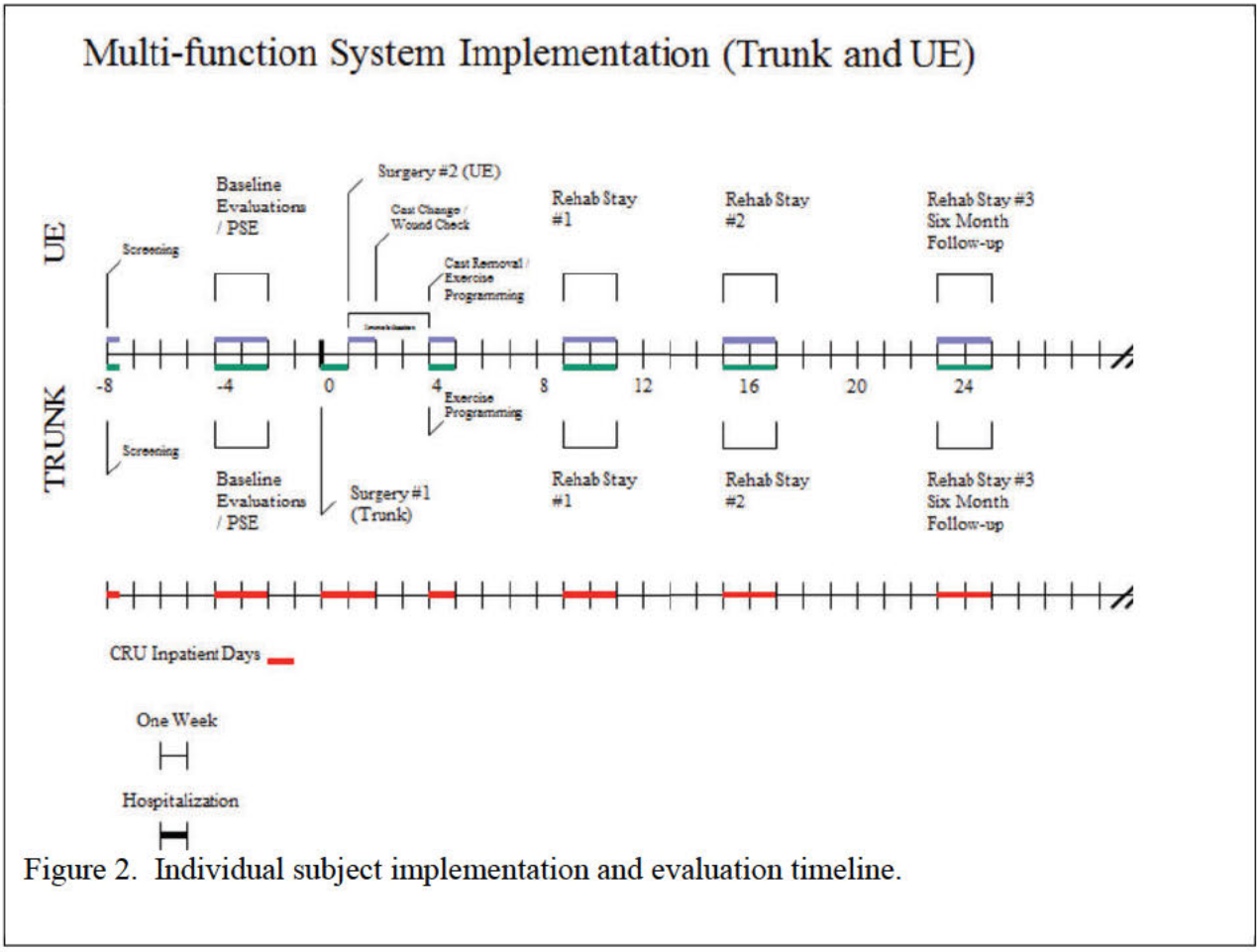

Figure 2. Individual subject implementation and evaluation timeline.

9.2. Screening

Please see the Screening Case Report Form. A comprehensive medical history and physical exam will be performed to ensure that the subject meets the selection criteria. Subject demographic data and medical and treatment histories will be obtained so that key factors that may contribute to clinical outcomes can be

considered. All medical records from the previous year will be obtained in order to record all medical interventions, with a focus on infection rates and general health. All medication records will also be obtained for that same period. In cases where additional information is necessary to establish a fit with inclusion and exclusion criteria, medical records from further back will be obtained – as early as from the time of injury. The purpose of these assessments is to demonstrate a stable physiological and functional status and to establish an average rate of health-related events prior to surgery. An assessment will also be done to establish the safe functioning of the NNP system with the subject's wheelchair, to assure electromagnetic compatibility.

Screening tests will include:

- Active and Passive Range of Motion
- Manual Muscle Test
- Stimulated Manual Muscle Test
- Pinch Strength, Sensation (two-point discrimination)
- Grasp-Release Test

Following the Manual Muscle Test and Stimulated Muscle Test, the targeted placement of electrodes and surgical plan are developed.

Surface-based myoelectric recording is used to determine the placement of the myoelectric electrodes for each subject [Knutson et al., 2004]. Prior to surgery, conventional pre-operative tests will be performed to establish that the subject is medically cleared for surgery (see Pre-Operative Laboratory Evaluation, below).

9.3. Pre-Operative Muscle Conditioning

Patients who demonstrate voluntary proximal muscle strength and range of motion that would enable them to make functional use of the neuroprosthesis will proceed to a muscle-conditioning phase. The goal of this phase is to increase the stimulated strength and fatigue resistance of the paralyzed muscles prior to surgery. Muscle conditioning is used to target the muscles with the weakest response to electrical stimulation. The conditioning is performed using conventional surface stimulation, with electrodes applied to the target muscles in the trunk and upper extremity. Surface electrodes are placed over the muscle belly or over the muscle innervation, and stimulation is applied daily using a conventional neuromuscular stimulator. After reaching sufficient strength, assessed as grades 3 to 4 with stimulation using a manual muscle test, the patient may be considered for surgical implantation.

9.4. System Customization

The NNP System has two important aspects that can be customized in order to maximize function for each subject. The selection of the number and placement of both the stimulating and recording electrodes can be customized to match the paralyzed/voluntary musculature of each subject. These decisions are made before surgery as part of the surgery plan, and are unchangeable after surgery (without additional surgery). The stimulus patterns that create the coordinated movement patterns, as well as the signal processing parameters for the myoelectric control

signal, must be customized. These parameters can be modified as needed once the subject begins attempting functional tasks, although in practice these parameters typically remain static after the first few months of training and use.

9.4.1. Need For System Customization

Traumatic spinal cord injury at the cervical level can result in severe paralysis and significant disability. Among the typical characteristics of SCI is the variable pattern of paralysis, partial paralysis and voluntary musculature that each individual presents with. Some of the differences among individuals can be attributed to their pre-injury physiology, such as their pre-injured muscle strength and innervation patterns. Other differences are attributable to factors that occurred at the time of trauma, such as the extent of upper motor neuron damage (degree of completeness of the injury) and extent of lower motor neuron damage (denervation). Finally, differences can be attributed to post-injury factors such as rehabilitation methods, personal motivation and degree of care, which can result in varying degrees of joint flexibility/contractures. Taken together, these factors require that any intervention must be customized to the individual in order to maximize the benefit. The NNP-UE System is designed to allow this customization within the framework of a well-prescribed decision-making procedure. This customization procedure allows both the clinician and the patient to make maximal use of the patient's remaining voluntary musculature and to couple that with optimum activation of their paralyzed musculature. This customization is also performed based on the goals of the individual. Thus, the outcome of the NNP-UE System customization procedure is a system that is optimally tuned to the individual, with the goal of maximizing functional independence.

9.4.2. Decision-Making Procedure

Key inputs to the customization process are the subject's voluntary strength, the subject's muscle excitability and the subject's functional goals. The former two inputs define the muscles need and the muscles available for activation. The latter input defines the types of movements needed. Based on these inputs, each functional movement pattern is evaluated and the primary target muscles are identified to provide that function. Frequently there are alternative muscles that can be used to substitute for, or enhance, the particular movement pattern. The pulse generator module has four channels of stimulation, and therefore the number of required stimulus channels is rounded up to the nearest multiple of four to define the total number of modules needed. Maximally, the NNP-UE configuration includes five pulse generator modules and two remote sensing modules. However, many subjects have residual voluntary function that obviates the need for a particular movement pattern, or the subject may have extensive denervation that limits the available stimulated muscles. Minimally, the NNP-UE System consists of at least one pulse generator module and at least one remote sensing module.

9.5. Pre-Operative Procedures

Prior to device implantation, a subject may be considered for surgical reconstruction. Such surgical procedures are individualized to the needs of each patient, and may

include arthrodeses, tendon transfers of muscles with upper motor neuron lesions, and tendon synchronization using side-to-side anastomoses. The objective is to provide a musculoskeletal system that can be efficiently powered by electrical stimulation using the fewest active channels of stimulation. These procedures can be performed prior to NNP implantation, or during the NNP implantation procedure. In performing these procedures, clinical surgical operative and post-surgical management protocols will be followed.

9.6. Pre-Operative Laboratory Evaluation

The following common tests are performed prior to surgery to determine the subject's medical suitability for surgery:

- Urinanalysis and urine culture and sensitivity
- CBC with differential
- ESR (erythrocyte sedimentation rate)
- Basic Metabolic Profile (includes Na+, K+, Cl, BUN, Ca, CO2, Creatinine, anion gap, glucose, estimated GFR)
- PT, PTT, INR
- Hepatic Function Profile (includes Total protein, albumin, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, ALT (SGPT), AST (SGOT))
- Hepatitis B (hepatitis B surface antigen)
- Hepatitis C (HCV)
- Nasal swab for culture and sensitivity
- HIV
- EKG
- CXR
- MRSA Screen (nasal swab)
- Dental Exam
- Renal and Bladder ultrasound
- Skin Assessment
- Pregnancy test

9.7. Device Implantation

Once the subject has completed the muscle conditioning and the surgical planning is complete, the NNP System is implanted in one or two procedures, typically lasting four to seven hours each.

The surgical implantation procedure will closely correspond to the procedure that has been utilized for similar systems and has been described in detail by Keith [Keith, et al., 1989] and has proven effective to date [Kilgore et al., 1997; Peckham et al., 2001; Peckham et al., 2002; Kilgore et al., 2008]. The surgery is performed under general anesthesia in a sterile field.

For electrodes and system components, incisions are made to allow surgical access to the chest overlying the pectoralis major muscle, the axilla and anterior deltoid

muscle, the antecubital fossa, the volar forearm, the dorsal wrist and the palm of the hand by extensive exposure. Exposure of the power module implantation site in the abdomen is also performed. Stimulating electrode locations are mapped using a temporary epimysial or intramuscular electrode probe with direct visual observation of stimulation of the muscle. Optimal electrode position is determined by observation of the muscle response with stimulation, with particular attention paid to the maximal force output, maximal selectivity (minimal stimulus spread to adjacent muscles), minimal change in force with changes in muscle length, and modest recruitment gain [Kilgore and Peckham, 1993]. The reference electrode (anode) is placed in contact with the tissue in the pocket prepared to receive the nearest stimulator module.

Electrodes are placed on the muscles necessary to provide lateral grasp, palmar prehension, ulnar-opposition grasp, power grip, elbow extension, forearm pronation, shoulder stabilization and trunk stabilization, following the pre-surgical plan as developed and described in Customization Decision-Making Procedure.

Intramuscular electrodes are inserted directly into the muscle belly using a probe and carrier technique [Memberg et al., 1994]. Epimysial electrodes are sewn in place on the muscle surface with non-absorbable braided suture. Electrode leads are tunneled to the location of each remote implantable device. Electrode placement and connections between devices are typically made distal to proximal.

MES recording electrodes are placed on or in the muscle in a similar manner. MES electrodes are generally placed just distal to the motor point of the muscle, as identified through direct electrical stimulation using an epimysial mapping probe. If sufficient signal can be obtained from the extensor carpi radialis, it is the preferred site for proportional control of grasp. Brachioradialis is an alternative that can be used when necessary. Additional MES electrodes can be placed on head or neck muscles, typically platysma and trapezius. Leads from the recording electrode are tunneled for connection to each remote sensing module.

The power module is placed in a subcutaneous pocket overlying the pectoralis major fascia or in an abdominal pocket. These locations are the same as those used for cardiac pacemakers, deep brain stimulators and drug pumps. The implanted devices are sutured in place to the underlying tissue with non-absorbable braided suture through suture loops on each component. Each remote module is sequentially connected to the more proximal remote modules by tunneling a network conductor cable (NC2) between incisions. A final network connection is made between the most proximal remote module and the power module. The entire system is tested through the wireless link to the Control Tower in order to identify proper communication between the implanted components. Each stimulating electrode is addressed and activated at a low level to verify conductivity.

Prophylactic antibiotics are administered one hour prior to surgery and continued for 48 hours post-operatively. Post-operatively, the arm is immobilized for three weeks to allow wound healing and encapsulation and stabilization of the electrodes and implant stimulator. When the cast is removed, active muscle stimulation and unloaded, unresisted exercise is initiated to build up fatigue resistance. Functional

use of the hand and the stimulation system is permitted at six weeks. Post-implantation radiographs are taken of the arm, shoulder and chest to document implant position.

9.8. Neuroprosthesis Programming and Training

After the healing is complete from surgery, it is necessary to establish the stimulation and control parameters that produce functional movements for each subject. The specific parameters are unique to each subject and depend on the placement of each electrode and the physiology of each muscle (strength, innervation status, etc.).

Maximum benefit from the neuroprosthesis requires tuning of the parameters involved in command algorithm processing and in the patterned electrical activation of the paralyzed muscles. The process of tuning is necessary because each patient presents with a unique array of voluntary muscle strength, passive and active range of motion, stimulated muscle response to stimulation and, most importantly, different functional goals and home/community environments. The primary goal of the neuroprosthesis programming procedure is to tailor the multiple system parameters to produce functional movements that are controlled as naturally as possible. Neuroprosthesis programming is an iterative process that actively involves the clinician/therapist and the patient in order to achieve the optimum results. Typically neuroprosthesis programming is performed over a period of a few sessions, each lasting a few hours, with patients spending ample time attempting a variety of activities to identify grasp and control features that need further tuning.

There are two major aspects of neuroprosthesis programming: control signal setup and grasp pattern setup. There are multiple steps to each of these aspects, and there can be interaction between the two, but in general it is possible to concentrate on each aspect individually. The grasp patterns are developed first, which then allows the patient to utilize these grasp patterns for practical testing during the control signal setup phase.

9.8.1. Grasp Pattern Setup

The methods for developing and customizing grasp patterns for each subject have been well-established in previous studies over the past 30 years [Kilgore et al., 1989; Kilgore and Peckham, 1993; Kilgore, 2000; Peckham et al., 2001] and consist of a two step process. In the first step, referred to as “electrode profiling”, the properties of the individual electrode-muscle units are characterized to describe the threshold level for activation and the maximum current level at which selective activation of the principal muscle is achieved. Unusual characteristics of the electrode-muscle response are also noted during this step, such as a highly non-linear recruitment or significant muscle length-dependent activation. These factors generally can be avoided by proper placement of the electrode during surgery. The electrode profile provides the grasp programmer with a complete picture of the

individual stimulated movements that are available for coordination into useful functional patterns.

Once the electrode profile is completed, the threshold and maximum stimulation parameters for each electrode are entered into a standard “grasp template” which establishes the activation of each of the muscles relative to the others as a function of the command input. The function that relates the proportional command input (0% (open) to 100% (closed)) to the stimulation level for each electrode is referred to as the “stimulus map” [Kilgore et al., 1989].

Only a single command governs the activation of all muscles in each grasp pattern. Multiple grasp patterns are generated, each providing a unique grasp function, such as a lateral pinch, palmar grasp, power grasp, etc.. Refinement of the grasp is accomplished by increasing or decreasing the stimulus parameters of individual muscles in order to achieve the desired coordination and smooth hand movement. This procedure has now become a standard procedure that is practiced by therapists in deploying clinical neuroprostheses [Peckham et al., 2001].

Grasp parameters are also used in an exercise mode in which the muscle is conditioned post-operatively in order to increase muscle strength and endurance. The muscle conditioning paradigm that we have utilized consists of ten cycles of each grasp pattern in which each cycle consists of one second of hand opening followed by a two second transition from open to close, followed by a one second hand closing, followed by a transition back to opening. This is conducted for both lateral and palmar prehension for a period of 50 minutes per hour. Generally, the subject is instructed to increase this exercise from one hour per day, up to as many hours per day as is convenient over approximately a two-month rehabilitation period. Most subjects, once they are actively using their neuroprosthesis functionally during the day, find that continued exercise is not necessary and that their stimulated muscles maintain good endurance with regular daily use only.

9.8.2. Control Signal Setup

Control signal evaluation and programming is performed to establish the parameters that describe the control algorithms, adjust the specific parameters for myoelectric signal processing, and establish the specific threshold and range values for customized control [Hart et al., 1998; Kilgore et al., 2008]. The NP functions that must be under the control of the user include: the selection of the grasp pattern (typically two to four grasp patterns are provided), the opening and closing of the hand in a proportional manner, and the ability to “lock” and “unlock” the hand so that a grasp can be maintained in a fixed position without the need for continued control input. In addition, it is desirable to enable the users to turn the stimulation on and off when needed. Finally, if patients are provided with elbow extension through triceps stimulation, forearm pronation, or shoulder/trunk stabilization, a control signal is needed to turn the stimulation on and off. If the user has sufficient control over the muscles providing MES, they may also gain some proportional control over these latter functions, such as the ability to control the level of triceps stimulation. These commands can be accomplished through the use of the myoelectric signal inputs, or

by depressing a button on the Control Tower (if desired). One MES channel is used to control grasp opening and closing, and is generally placed on the most distal upper extremity muscle under voluntary control, typically the extensor carpi radialis longus (ECRL) or brachioradialis (Br). Additional MES channels are used to provide state or logic commands, such as system on/off and selection of the grasp pattern. These signals are typically derived from myoelectric signals from proximal muscles, such as trapezius or platysma, and can also be derived from an external switch input located on the control tower.

The myoelectric control algorithm must be customized for each patient in order to maximize functional benefits of the neuroprosthesis. First, patients are asked to alternate between maximal voluntary contractions of the control muscles and periods of relaxation while the computer records the signals from each myoelectric recording electrode. This allows the software to identify the magnitude of signal obtained from each recording electrode. The first parameter to be set is the MES scaling parameter. The scaling establishes the threshold MES value that corresponds to 0% command range and the maximum MES value that corresponds to 100% command. MES values below the threshold all correspond to 0% command and MES values above the maximum established by the scaling saturate the command at 100%. It is not possible for the command value to be outside of the range 0 to 100. Note that if the range is set very narrow, with the maximum value nearing the threshold value, the command effectively becomes an “on/off” switch, where the command is either 0% or 100%.

If the control muscle is to be used as a proportional signal for control of grasp opening and closing (or similar functions), then the next step in the control setup is to establish the adaptive stepsize filter characteristics. The adaptive stepsize filter is well-suited for neuroprosthetic control applications because it combines a smooth, steady signal with a minimal response delay during rapid movements. The stepsize filter allows increasingly larger step increases in the command level as long as the incoming signal continues to change in the same direction. When the incoming signal changes direction, the allowed stepsize is reset to the smallest value. Using these two principles, large rapid fluctuations in the command are smoothed to an insignificant ripple, whereas large movements in a single direction are reproduced with very little delay due to the filter.

If a control muscle is to be used to produce a logic command, the incoming myoelectric signal is processed differently. For use as a logic command, it is important that the subject can generate the signal easily, but the signal must be unique enough that the subject does not inadvertently generate the signal during unrelated tasks. This can be accomplished very successfully by requiring the logic signal to meet three characteristics. First, a “quiet period” is required in which the incoming signal must stay below a threshold. This prevents logic signals from being detected incorrectly in the midst of ongoing functional tasks. The duration of the quiet period can be set as needed, but is typically less than one second. Second, the change in the incoming signal (i.e. velocity) must exceed a “rising threshold”. Once the rising threshold is exceeded, the third criterion is that the change in the incoming signal must drop below a “falling threshold” within a fixed

period of time. All of these parameters can be tuned to the individual user so that they can easily generate this signal reliably. Once subjects gain experience generating this signal, they are able to reliably generate the signal when desired, but rarely generate the signal unintentionally.

Once the basic signal processing parameters are established, patients are then instructed in how to make the desired control movements, and the ensuing signal is recorded. Biofeedback, supplied on screen is used to assist in training patients regarding their success or failure in generating the desired signals. The goal of this setup phase is to determine the range of useful signal amplitudes for each myoelectric channel. Patients will also be asked to perform functional movements that could potentially interfere with the control signal (such as arm movements if the electrode is located on the trapezius, or facial expressions if the electrode is located on the platysma), resulting in further refinement of the control signals. An initial control algorithm is developed based on the empirical observations by the programmer. Patients are then given the opportunity to evaluate the performance of their neuroprosthesis by performing simple tasks. During the operation of the neuroprosthesis, the patient's control signals are continuously monitored. Information regarding the patient's success or failure in generating the appropriate control is also monitored by the clinician. The clinician continues to make adjustments to the parameters and repeat testing in an empirical manner until the patient has good control of their grasp functions.

9.9. Subject Assessment and Follow-Up

Study participants will be evaluated prior to surgery, and during rehabilitation following surgery (three one-week sessions, final session at six months post-implant). Technical assessment of system performance will be performed at 12 months post-implant and annually for at least three years post-implant.

We have utilized the International Classification of Function (ICF) (developed by the World Health Organization) [Stucki et al., 2002] as a conceptual framework for development of the outcome measures proposed in this study. The ICF is neither an assessment nor a measurement tool in itself, rather it is a useful conceptual model that can be applied to assessment, outcome measurement, and research. Consequently, the ICF can be used to guide intervention and to structure the interpretation of outcomes measurement in the context of improving function in individuals with tetraplegia [Sinnott et al., 2004; Bryden et al., 2005]. The primary domains of the ICF are body functions and structures (formerly impairment), activities (formerly disability) and participation (formerly handicap). Outcome measures specific to each ICF domain have been selected. The primary efficacy endpoint measure is the ability to grasp, manipulate and release objects, as measured by the Grasp Release Tests. Detailed testing is described in the Study Endpoints section, below.

At every visit post-implant, the subject is instructed to bring all NNP System components with them. The coil and pad is inspected for signs of wear or damage. The Control Tower is also inspected for signs of damage. If these components are

damaged or worn, they will be replaced. Subjects will be asked if they have experienced any problems with the technology, including possible interference from other wireless devices. If subjects report problems, they will be reported using the Adverse Event Form.

10. STUDY ENDPOINTS

Formal hypothesis testing and calculation of a study sample size will not be conducted as part of the Early Feasibility IDE due to the nature of the study itself. However, results from the Early Feasibility study will be used to finalize the choice of primary endpoint, establish a study hypothesis, and justify the final sample size for the pivotal clinical study. We will perform the outcome assessments that are expected to be part of the clinical trial, however, some of these studies may be reduced, eliminated, or combined in order to reduce the study burden on the subject and maximize follow-through.

10.1. Proposed Primary Effectiveness Endpoint: Grasp and Release Test (GRT)

The Grasp and Release Test (GRT) [Wuolle, 1994; Smith et al., 1996; Carroll et al., 2000; Taylor et al., 2002; Mulcahey et al., 2004], developed at the Cleveland FES Center, has been utilized by multiple centers to show improvements in hand function after implantation of a neuroprosthesis and tendon transfers [Peckham, 2001]. This pick-and-place test requires the participant to unilaterally acquire, move, and release six objects varying in weight and size. The objects are: 1) a small peg, 2) a wooden cube, 3) a small juice can, 4) a videotape, 5) a paperweight (~1000g) and a simulated fork task (spring-loaded plunger). The number of objects that the participant can successfully manipulate, as well as the number of repetitions achieved in a 30-second trial, are scored. Success in manipulating each object in the GRT is defined as the ability to pick up and place the object at least once within 30 seconds.

The primary baseline for assessment of the GRT is the performance of the subject with the neuroprosthesis turned off. This provides the most direct comparison of the improvement provided by the GRT. Performance on the GRT is also measured prior to implantation of the NNP, and this data can serve as a second baseline. Our previous studies utilizing the GRT are directly analogous to the NNP study. In previous studies, there is a slight increase in GRT performance when the post-surgery results with the neuroprosthesis turned off are compared to the pre-surgery results. This slight increase is due to any tendon transfers performed at the time of the NNP implantation, since these can provide function even when the stimulation is turned off. **The primary endpoint of this study is the change between GRT performance at the post-surgery time point alone.** As a secondary measure, GRT performance pre-surgery can be compared with GRT performance post-surgery with the use of the neuroprosthesis. This latter measure is more likely to show improvement and therefore we selected the most conservative estimate as our primary outcome measure (post-op with vs. post-op without).

The psychometric properties of the GRT were established by Mulcahey et al.[2004], showing good test-retest reliability with intra-class correlation (ICC) coefficients ranging between 0.87 and 1.00.

10.2. Proposed Primary Effectiveness Endpoint: Trunk-Stimulated Reaching Ability

Using a VICON system for motion analysis, subjects will perform forward bimanual reaching maneuvers toward pre-determined targets placed in the testing volume. Targets will consist of reflective spheres at heights from below knee-level to about head-level just out of reach. Subjects will reach to a target, pause and then return to the starting position. Trials will be repeated with and without stimulation in random order and while carrying various loads up to a maximum of 25% of shoulder strength. **Measures of absolute and relative reach length will be derived from each trial.** Absolute reach length includes the contributions of both the trunk and arms, while relative reach length measures the contribution of the arms alone. Effects of stimulation on lateral unilateral, one-handed reach will be assessed in a similar manner. Lateral reach will be evaluated by placing the targets in line with the shoulders in the coronal plane.

10.3. Proposed Primary Effectiveness Endpoint: Combined Hand and Trunk Performance

We will use the Early Feasibility Study to establish an appropriate endpoint that captures functional performance with both the hand and trunk systems working simultaneously. We anticipate using either a modified GRT test that includes a reaching component, or the Activities of Daily Living (ADL), with an emphasis placed on activities that require reaching. Comparisons will be made at the 6-month follow-up point with both hand and trunk stimulation ON v. OFF, as well as with.

10.4. Primary Safety Endpoint

10.4.1. Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Requires overnight hospitalization
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is life-threatening or results in death

Serious Adverse Events will be documented at each follow-up session.

10.4.2. Device Complications

A Device Complication (DC) is defined as any malfunction, failure to operate as defined by the Instructions for Use, technical problem, or operator error associated with the use of the device.

Device Complications will be documented at each follow-up session post-implant. It should be noted that the process of recording electrode thresholds provides a complete analysis of the proper function of the implantable components from a technical standpoint. Thus, if any electrodes

are broken or dislodged, these will be identified through the electrode threshold process. The clinical investigator will classify the cause of any adverse event as either device-related, procedure-related, not related to device or procedure, or unknown.

10.5. Secondary Endpoints

SECONDARY ENDPOINT	COMMENTS
Active and Passive Range of Motion (A/PROM)	A/PROM will be measured for the entire upper extremity including the shoulder according to standard occupational therapy techniques [Trombly and Scott, 1989].
Manual Muscle Test (MMT)	MMT will be performed for the entire upper extremity including the shoulder according to standard occupational therapy techniques [Kendall, 1993].
Muscle Excitability	The innervation status of the paralyzed muscles in the arm and hand will be determined by applying surface electrical stimulation using a commercially available muscle stimulator with a maximum output of 100mA, 300μs and 50Hz. The results will be graded according to manual muscle testing guidelines. Paralyzed muscles that respond to stimulation with a grade 4 or 5 response will be candidates for implantation.
Pinch Strength	Pinch force will be measured using a modified pinch meter (B & L Engineering, Santa Fe Springs, CA) with metal bars added to extend and enlarge the grasping surfaces of the meter. Both lateral and palmar prehension will be measured with the neuroprosthesis turned on and turned off.
Sensation	Sensation in the hand will be assessed using a two-point discrimination method [Callahan, 1990]. While sensation is not expected to change as a result of the neuroprosthesis, the information is needed to augment injury level classification.
Seated Posture	Changes in seated posture with FES will be quantified with the VICON motion capture system in the Motion Study Laboratory. Passive reflective markers will be placed on the body (nominally on the occiput, forehead, sternum and T1 vertebrae, and bilateral ASIS, PSIS, acromium, scapular spines and midway between ulnar & radial epicondyles). Subjects will sit without a backrest on an adjustable mat table with the feet flat on the floor and femurs parallel to the support surface while each experimental condition (trunk stimulation ON and OFF) is repeated. Indicators of seated posture and trunk alignment (pelvic tilt, forward head position, shoulder height and symmetry) will be determined by the relative positions of the appropriate markers. Additionally, AP and Lateral spinal x-rays will be taken both with and without stimulation.
ADL Abilities Test	The ADL Abilities Test was originally developed by researchers at the Cleveland FES Center to measure differences in activity performance with and without a hand neuroprosthesis [Stroh et al., 1994; Kilgore et al., 1997; Peckham et al., 2001; Bryden et al., 2008]. Scoring is based on an activity analysis approach. The activities, which are chosen by the participant, are broken down into phases, and each phase is scored for the amount of assistance the participant uses.

Participant Satisfaction Survey	The Neuroprosthesis Satisfaction Survey was developed by researchers at the Cleveland FES Center and was utilized as part of a previous multi-center study [Wuolle et al., 1999; Peckham et al., 2001].
Device Usage Log	The NNP System has datalogging capabilities internal to the Control Tower. We will record the date and time of the start and stop of all charging activities. Data will be retrieved at each visit.

11. STATISTICAL METHODS

11.1. Total Projected Sample Size

For the purposes of the Early Feasibility study, a sample size calculation will not be performed.

11.2. Handling of Missing Data

Every attempt to capture required information missing from the CRFs will be made. No imputation or substitution of missing data will be conducted.

11.3. Descriptive statistics

Because of the few number of subjects treated, individual subject results will be presented separately for all primary and secondary outcome measures. Where statistically appropriate, measures of central tendency (means, medians) may be calculated.

12. ADVERSE EVENTS

For the purpose of this study, adverse effects will be recorded as either an Adverse Event or a Device Complication, or both, if applicable. All AEs occurring during the study will be recorded on the appropriate case report forms (CRFs).

12.1. Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient enrolled in a clinical investigation who has been administered study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational device, whether or not related to the investigational device. Patients will be encouraged to report adverse events spontaneously or in response to questions during follow-up sessions. For each AE volunteered by the patient, the Investigator should obtain all the information required to complete the Adverse Event page of the CRF:

- Date of onset
- Description of adverse event
- Clinical severity of the event
- Description of any actions required and associated outcome
- Date of resolution of the adverse event
- Whether or not the effect was serious and/or unanticipated
- Relationship between the adverse event and the device.

  The Investigator will use the following definitions to assess the relationship of the **adverse event to the device**:

RELATIONSHIP	DEFINITION
Definite	Adverse event that has a strong temporal relationship to the study treatment or recurs on re-challenge and for which there is no other plausible explanation or etiology.
Probable	Adverse event has a strong temporal relationship to the study treatment and another etiology is unlikely or significantly less likely.
Possible	Adverse event has a strong temporal relationship to the study treatment and an alternative etiology is equally or less likely compared to the potential relationship to the study treatment.
Not Related	Adverse event that is clearly due to other factors such as underlying or concurrent illness or effect of another device and for which no temporal relationship to study treatment exists.

- Relationship between the adverse event and surgical procedure.

  The Investigator will use the following definitions to assess the relationship of the **adverse event to the surgical procedure**:

RELATIONSHIP	DEFINITION
Definite	Adverse event that has a strong temporal relationship to the surgical procedure or recurs on re-challenge and for which there is no other plausible explanation or etiology.
Probable	Adverse event has a strong temporal relationship to the surgical procedure and another etiology is unlikely or significantly less likely.
Possible	Adverse event has a strong temporal relationship to the surgical procedure and an alternative etiology is equally or less likely compared to the potential relationship to the surgical procedure.
Not Related	Adverse event that is clearly due to other factors such as underlying or concurrent illness or effect of another device and for which no temporal relationship to the surgical procedure exists.

All AEs, regardless of seriousness, severity, or presumed relationship to study device or related procedures, will be recorded using medical terminology in the source document and on the adverse event CRF.

12.2. Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Requires overnight hospitalization
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is life-threatening or results in death

All SAEs will be reported immediately and documented per protocol. The Investigator will also report the SAE to the reviewing IRB in accordance with their guidelines.

Details about the onset of the SAE, its progression, diagnosis and treatment will be collected from the patient and recorded in the source document. Likewise, any tests that are conducted to assist with the diagnosis will be described in the patient's source documents

12.3. Device Complications

A Device Complication (DC) is defined as any malfunction, failure to operate as defined by the Instructions for Use, technical problem, or operator error associated with the use of the device. For each device complication, the Investigator will report:

- Description of Device Complication
- Date complication was first noted
- Clinical consequences, if any (to be reported on Adverse Event form)

12.4. Unanticipated Adverse Device Effects

An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

If there is an Unanticipated ADE during the course of this clinical trial, regardless of its association with the study device or related procedure, the Investigator will submit a report to the reviewing IRB as soon as possible.

All information on the circumstances of the event, including a death certificate and an autopsy report (if applicable), will be documented. A statement of the Investigator's opinion as to whether or not the event was device and/ or procedure-related will be included.

12.5. Reporting Procedures

Should an UADE occur with the NNP System, it is the responsibility of the investigator to conduct an evaluation of the event and to report the. This report will be sent to the FDA and the reviewing IRB. If the investigator determines that this UADE represents an unreasonable risk to the clinical investigation population, the study will be terminated. A terminated study may be reinitiated based on approval of the reviewing IRBs and the FDA.

A report detailing device experience will be generated from as required by the FDA or as deemed appropriate by the investigator, reviewed by the Clinical Events Committee, and distributed as necessary to the IRB.

12.6. Clinical Events Committee

An independent Clinical Events Committee will be formed that consists of a minimum of three (3) members who have experience in the spinal cord injury and neuroprosthetics. This committee will be responsible for reviewing all adverse events (including serious adverse advents and unanticipated adverse events, whether serious or not) and will have the authority to over-rule site-reported events as necessary and appropriate.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Device Accountability

It is the responsibility of the Clinical Investigator to ensure that all study devices received at the clinical site will be inventoried and accounted for throughout the study.

13.2. Informed Consent

Before enrollment in the study, each patient (or a legally authorized representative) must sign the informed consent and other locally required documents after the nature of the study has been fully explained to them. The consent form must be signed prior to the performance of any study-related activity. The consent form will be approved by the reviewing IRB prior to use. One copy of the completed informed consent form will be given to the subject, one copy will be placed in the subject's medical record as a source document, and one copy placed with the subject's investigational records.

13.3. Patient Confidentiality

All information pertaining to each subject will be held on a confidential basis. This information may be subject to audit by regulatory authorities and, where appropriate, authorized agents will have the right to inspect and copy information in patient files.

13.4. Regulatory Documentation

The Investigator will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate immediate hazards to human subjects. These reports should be made in accordance with the policies and procedures of the Investigator's IRB.

The Investigator will also report to the IRB, at least annually, on the progress of the investigation. Continuing IRB review and renewal of approval should be documented by a letter from the IRB. Notification to the IRB by the Investigator within 3 months after completion, termination, or discontinuation of the study at the specific clinical site must be documented.

13.5. Study Monitoring

Monitoring functions will be performed in compliance with recognized Good Clinical Practices, the FDA's "Guideline for the Monitoring of Clinical Investigations" (1988), and as outlined in 21CFR §812.43(d) and 21CFR §812.46

13.6. On-Site Audits

The Investigator shall permit authorized FDA employees to inspect and copy records that identify subjects.

13.7. Case Report Form (CRF) Completion

Case report forms are provided for each patient, and will be filled out in ink.

All case report form corrections are to be reviewed by the Investigator or other appropriate clinical site personnel. The Investigator is ultimately responsible for all data entries.

The study monitor(s) will review the case report forms and determine their acceptability. Completed case report forms will be collected by or submitted to the Sponsor.