Providing Brain Control of Extracorporeal Devices to Patients With Quadriplegia

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Table of Contents

Study Synopsis

Brain signals may be used to control extracorporeal devices such as robotic effectors, prosthetic limbs, or computer systems. For paralyzed patients, a device which implements such a possibility could represent an important step forward in providing some independence and the ability to interact with the environment. This prospective, longitudinal, single-arm feasibility study will be used to evaluate the safety and effectiveness of the Neural Prosthetic System (NPS), a device designed to record brain signals from the cortex, to control physical and virtual effectors. The NPS uses electrodes which are already approved by the FDA for implantations of less than 30 days; an Investigational Device Exemption has been obtained from the FDA which allows implantation of 53 weeks in two subjects. While the NeuroPort Array has been used in other longitudinal clinical studies with similar applications, the primary advantage and differentiating feature of our study is that we will use the posterior parietal cortex to extract cognitive brain signals representing intention and planning of reaching and grasping. This study is not intended to provide immediate treatment or benefits to its participants. However, the long-term implications of the study objectives could enable new technologies to provide assistance to people suffering from paralysis.

NPS Feasibility Study	
Test Device	Neural Prosthetic System, consisting of two NeuroPort Arrays (Blackrock Microsystems, Salt Lake City, UT)
Cohort	People with high cervical spinal lesion (i.e., C4 or above)
Primary Objectives	To assess the safety and evaluate the effectiveness of the NPS as a method for paralyzed people to interact with their environment.
Device Configuration	The NPS consists of two NeuroPort Arrays. Each NeuroPort Array consists of an electrode array (100 electrodes in a 10 x 10 configuration with dimensions 4 mm x 4 mm x 1.5 mm (W x H x D); a titanium percutaneous connector, 19 mm diameter at the base.
Study Design	A longitudinal clinical feasibility study. Subjects participate in study sessions 3-5 times per week at RLANRC (their place of normal clinical care) during the study period. Each subject participates for a total of 66 weeks, including surgeries and follow-up care; the study period is 53 weeks.
Number of Subjects to be Enrolled	Two subjects will be enrolled.
Number of sites	One site, with multiple supporting institutions.
Key Inclusion Criteria	Paralysis (high cervical spinal lesion, C4 or above) initiated at least one year prior and stable for at least 3 months prior.
Key Exclusion Criteria	Active psychiatric or medical illness which precludes surgery, stable participation in study sessions, or which requires MRI or other contraindicated procedure during time enrolled.
Primary Efficacy Objective, Analysis, and Methods	The primary effectiveness objective is to evaluate the long-term effectiveness of the NPS. The primary outcome variable is the accuracy with which tasks are performed during study sessions, which will be compared to the level of chance. The secondary outcome variable is scoring on the Action Research Arm Test, a standard test used in occupational therapy to measure upper extremity limb function following cortical damage. The tertiary outcome variable is the quality-of-life index, measured before and after the study.
Primary Safety Objective, Analysis, and Methods	The primary safety objective is to evaluate the safety of the NPS. The primary outcome variable is the presence of infection or irritation around the implant site. The secondary outcome variable is the Severe Adverse Event (SAE) rate measured per subject as a percentage of implant-days. These factors will be measured during clinical follow-up care using standard observations and exams.

1.0 Background and Hypothesis

1.1 Clinical Target

The number of patients suffering from some form of paralysis in the United States alone has been estimated to be from 1.7 million (U.S. Dept. Health Human Serv. 1995) to 5.6 million (Christopher & Dana Reeve Found. 2009). Paralysis can result from spinal cord lesion and other traumatic accidents, peripheral neuropathies, amyotrophic lateral sclerosis, multiple sclerosis, and stroke. Another 1.4 million patients have motor disabilities due to limb amputation (U.S. Dept. Health Human Serv. 1995). A majority of these patients still have sufficiently intact cortex to plan movements, but they are unable to execute them. Thus they are candidates for assistance using cortical neural prosthetics.

Many studies have extracted motor execution signals from motor cortex in nonhuman primates and decoded them to predict and/or effect desired movements of a physical or virtual effector. In these studies, it was often observed that the monkeys quickly learned that they did not need to actually move their limb to bring a cursor or device under brain control. We refer to this as cognitive control, in which brain signals not directly related to executing a movement can nonetheless be harnessed for the task. This control can be derived from motor imagery, planning, attention, decision making, or executive control, to name just a few of the cognitive signals that are potentially useful for neural prosthetics. The distinction is not the brain location of the recording but rather the type of signal that is being extracted. Cognitive neural prosthetics tap into brain signals that are neither motor execution commands nor sensory signals, but rather represent higher brain functions such as intention, multi-effector and sequential movement planning, attention, decision making, executive control, emotions, learning, and speech. Scientific understanding of the functional organization of cortex helps to guide the placement of electrodes and the choices of decoding algorithms.

Once decoded, neural signals can be used to control extracorporeal devices such as robotic effectors, prosthetic limbs, or computer systems. Recently, the BrainGate study demonstrated cortical control of a computer cursor in human subject tests with severely paralyzed individuals. This milestone study marked a significant advance in the feasibility of neuromotor prostheses. However, the results obtained in that study (now in a second phase of clinical trials, called BrainGate2) decoded motor execution signals, which is slower than decoding movement goals and other high-level cognitive movement processes.

1.2 Study Overview

The proposed study is investigator-initiated and led by Dr. Richard Andersen at Caltech. The device being tested is the Neural Prosthetic System (NPS), which consists of two microelectrode arrays (NeuroPort Array, Blackrock Microsystems, Salt Lake City, UT) to be implanted in the brain and two sets of recording electronics (NeuroPort Biopotential Signal Processors, Blackrock Microsystems, Salt Lake City, UT) to amplify and record the neural signals. One microelectrode array will be implanted in Brodmann's area 5 (BA5), and the other will be implanted in the anterior intraparietal (AIP) area. The NeuroPort Arrays, which are currently FDA-approved for implantations of less than 30 days, will be implanted for a period of 53 weeks. Two subjects will be enrolled into the study. The NPS will be used to allow study participants to control virtual and real world objects using imagined movements of their arms and hands. While the NeuroPort Array has been used in other longitudinal clinical studies with similar applications, the primary advantage and differentiating feature of our study is that we will use the posterior parietal cortex to extract cognitive brain signals representing reach intention and planning. Therefore, the novelty in our study is twofold: (1) implantation for longer than 30 days, and (2) implantation into the posterior parietal cortex.

1.3 Background and Review

1.3.1 Chronic Implantation of NeuroPort Arrays in Humans

The NeuroPort Array is currently under 510(k) clearance by the FDA for human implantations to record and monitor neural activity for less than 30 days. The device has been cleared under IDE status to be chronically implanted in humans as part of the BrainGate and BrainGate2 clinical studies (1-8). The first subject (S1) of the Braingate clinical trial was implanted in June 2004, after three years of paralysis, with a NeuroPort Array located in the M1 arm area, with no reported incidence of adverse events during surgery or post-operative care (2, 8). A second subject (S2) was implanted in which electrical contacts had to be repaired, which caused a delay of 7 months before recording could begin, and was a possible cause for signal loss at month 11 (2). In both subjects,

multiple units were recorded (S1: 26.9 ± 14.2 units; S2: 53.2 ± 6.3 units) over several months well after the 30-day post-implantation mark (2). Over the course of nine months after implantation, S1 learned to use neural activity to perform a variety of daily tasks such as opening email and operating a television (2, 8). A third subject (S3), enrolled nine years after brainstem stroke, and a fourth subject (S4), enrolled six years after being diagnosed with amyotrophic lateral sclerosis (ALS), learned to use their neural activity to control a computer cursor over the course of 1003 days (S3), or 231 days (S4), after implantation (3-8).

In the BrainGate studies, NeuroPort Arrays have been implanted in the left precentral gyrus, in the M1 arm area knob. It is well known from nonhuman primate work that neurons in this region process arm reaching trajectories (9, 10); however, an important result of the BrainGate studies is that despite paralysis in the subjects, this cortical area has continued to process movement trajectories. Furthermore, in recent results documenting performance of online, closed-loop brain control 1000 days after implant, a subject achieved greater than 90% success rates while moving a cursor to targets on a screen (7). These results suggest that neural interfaces can (i) operate successfully over years; and (ii) provide sufficient performance to interact with computers in meaningful ways (2, 6, 7).

1.3.2 Posterior Parietal Cortex

In both nonhuman primates and humans, parietal cortex is traditionally thought to lie in the dorsal visual pathway encoding either spatial localization (11), or, alternatively, visual guidance of action (12). The posterior parietal cortex (PPC) is located between the occipital lobe (visual cortex) and postcentral gyrus (somatosensory cortex), and thus is naturally situated to process sensory inputs and project outputs to motor and pre-motor areas (13). Such high-level, multimodal processing of sensory inputs and motor outputs is one reason why we consider these signals as ideal candidates for cognitive control of neural interfaces: whereas motor cortex executes limb movement trajectories, the PPC processes plans which are then transferred to motor cortex for execution (14). Moreover, recent research suggests that PPC can provide a larger degree of useful prosthetic control signals as a result of its being situated at the interface between sensory and motor systems.

The posterior parietal cortex (PPC) is involved in transforming sensory inputs into plans for action – so-called sensory-motor integration (15-17). It is separated by the intraparietal sulcus into the superior parietal lobule and the inferior parietal lobule. Within the intraparietal sulcus, subregions have been implicated in planning eye movements (lateral intraparietal area, LIP) (18), reach movements (parietal reach region, PRR, medial posterior bank of intraparietal sulcus comprising both medial intraparietal (MIP) and V6a areas) (19), and grasping (the lateral anterior intraparietal area, AIP) (20). Brodmann's area 5 occupies the superior parietal lobule, and neurons within that area are active during sensory-motor integration and motor planning for reaches (13, 21-24). In particular the dorsal aspect of area 5 (area 5d) has been implicated in reach planning (25). The high-level, abstract nature of signals in these cortical areas is underscored by observations that plans can be formed and cancelled without execution (15, 26, 27), and that intended reach activity in PRR is coded in visual rather than limb coordinates (28). In contrast, area 5d, which is believed to be positioned downstream of PRR, codes reaches largely in limb coordinates (29, 30). PRR, AIP, and BA5 are particularly relevant to this application because reaching, grasping, and sensory integration for planning and guidance of these movements are integral components for the control of brain-machine interface effectors.

Local field potentials (LFPs) are a continuous signal representing the sum of electrical activity in the brain tissue near an electrode. We have shown that temporal structure in LFPs varies with planned or executed motor behavior (31), and found similar structure in LFPs recorded from LIP during saccade planning (32). Furthermore, we have shown that LFPs can support neural interface decodes as well as neuronal spiking (33-35), and in fact provide signals that are complementary to spikes. LFPs recorded from PPC encode behavioral state with fewer channels than spikes, whereas spikes provide direction of reach information with fewer channels than LFPs (31). Because LFPs are a summed signal, they may be less susceptible to degradation due to scarring (34, 36). Furthermore, LFPs are more robust to array micro-motion (e.g., from sneezing), which can affect single unit sorting assignments. Because of their stability, consistency, and potential for contributing to a neural interface, these signals may be a useful component of neural control.

In human as in monkey, a number of PPC subregions have been identified which are activated for visually guided actions such as reaching and grasping. Some of these areas, based on cytoarchitectural, neuroimaging, and neuropsychological data, have been tentatively identified as homologues of well-studied nonhuman primate areas PRR, AIP, and BA5 (37-51). The activity of human PPC appears to retain desirable qualities of monkey PPC which make this cortical area an ideal candidate for cognitive neural prostheses (40, 43). Neuroimaging studies

with human subjects have demonstrated that activity within the posterior parietal cortex, including areas accessible by the NeuroPort Array along the intraparietal sulcus, can be used to decode reach and grasp activities (50).

1.3.3 Adverse Information

Implantation of the NeuroPort Array requires a craniotomy; blunt dissection of the arachnoid space to separate the dura mater from the skull; incisions in the dura mater, and, finally, cortical insertion through the pia mater. During insertion, electrodes penetrate the neural tissue and cause local edema in the brain tissue. These features are common to many styles of electrodes which are designed to record the activity of single units from within the cortex, and so studies of other penetrating electrodes may be useful in understanding mechanisms in play when the NeuroPort Array is implanted. Acutely, local edema and hemorrhage are observed after implantation; these effects heal within weeks (52). Over the first several months, the tissue response to intracortical electrodes is a compact cellular sheath containing astrocytes and microglia (53). Persistent inflammatory reaction may be responsible for a reduced density of neurons in the region of tissue near the electrode (52-54). This phenomenon is not unique to microelectrodes for recording neural activity; it also occurs around the shank of electrodes used for deep brain stimulation (55). The foreign body response has been implicated as one factor in a reduction of recording performance over time for neural implants (52). This scarring tissue may contribute to varying degrees of electrical isolation of implanted electrodes from tissue, reducing the sensitivity of the electrode to biopotential signals generated in the surrounding cortex. One study using CerePort Arrays found a decline in the amplitude of action potential signals of 2.4% per month over as many as 31.7 months in three animals (56). These factors represent a challenge for neural interfaces and for this study. Importantly, despite these factors, it appears that neural interface control with chronic CerePort or NeuroPort Array implantations is still possible (7, 56). None of the authors of these studies indicate whether their investigations were conducted under GLP.

1.3.4 Summary of Background Material

The large body of work describing the nature of PPC activity in both nonhuman primate and humans during reaching and grasping leads to several conclusions regarding its value for brain-machine interfaces:

- Decodes of goals are very fast, in the order of 100 ms, which provides more rapid goal acquisition than primary motor cortex (14).
- Trajectories can be decoded with similar fidelity to M1 (57-59).
- At least two sequential goals can be represented and this feature can augment decoding performance of sequential limb movements (60)
- Goal and trajectory information when combined provide better decoding of trajectories than trajectory information alone (57).
- The representation of bilateral arm movements within a single hemisphere can provide bimanual control from a single implant (61, 62).
- The anterior intraparietal area (AIP) represents grasp shape which may reduce the number of cells needed to decode grasping (63, 64).
- PPC has stronger local field potential (LFP) signals than motor cortex (65) and LFPs can provide robust information on behavioral.

In short, cognitive signals in PPC which perform multimodal sensory-motor integration are ideal candidates for control signals in paralyzed patients (14, 34, 66, 67). Moreover, PPC can provide not only the signals found in motor cortex, but also high-level cognitive motor control signals, particularly those related to the goals of movement. One advantage of this multiplicity of signals is that a single implant can allow for a wider variety of control variables thereby improving the range and effectiveness of prosthetic control.

1.4 Risk Analysis

This early feasibility study is intended to evaluate the safety and effectiveness of the NPS, and thus is not intended to immediately provide the full benefits of direct brain-control of a prosthetic device to the subjects. The most serious risks to the subjects include those associated with anesthesia, brain surgery, and infection around the percutaneous connector. However, we believe the long-term benefits of the study outweigh the risks to the subject. This section will present an analysis of the risks to the subject associated with this study, specific plans to mitigate these risks, and benefits expected to be derived from this study.

This study will include two (2) subjects (selection criteria outlined in Section 5.0). It is expected that a caregiver will be available and involved in daily wound care and monitoring of the subject's wellbeing.

1.4.1 Risks Associated with Related Clinical Procedures

Components of this study which generate the majority of risk to the subject include the implantation and explantation surgeries, and the percutaneous connector. Given the early stage of clinical development for the device investigated in this study, it may be useful to examine other procedures and operations which include similar components. For example, bone-anchored hearing aids (BAHAs) rely on a titanium fixture similar to the titanium percutaneous component (the percutaneous connector) used in this study; rates of infection for BAHA devices have been reported in the range of 1.0% to 5.0%, with other complications (<1%) including persistent pain, granulation tissue, and persistent bleeding (68-71). Infections which occur as a result of neurosurgery are potentially severe, but have a low incidence rate of 1.7% to 2.6% in the United States (72-78). Placement of foreign bodies (specifically, shunts), CSF leakage, age, and duration of surgery have all been implicated as being significantly associated with surgical site infections for craniotomies and other neurosurgeries (73-75, 77). Prophylactic antibiotics may play a role in mitigating the risk of infection (73). Anticipated adverse events associated with implantation of leads for epilepsy localization procedures include hemorrhage (0.8% to 2.5% of patients), infection (1.8% to 9.1%) and permanent neurological complications such as hemiparesis, aphasia, apraxia, Gerstmann syndrome, and other sensory and motor deficits (0.6% to 1.5%; transient deficits occur somewhat more frequently). Resection of epileptic tissue is associated with hemorrhage (0.7%) and infection (1.0%) and neurological deficits (about 3.3%), such as language, visual field, and motor deficits. Deep Brain Stimulation (DBS) systems are associated with hemorrhage (1.1% to 3.9%), infection (1.7% to 4%), and neurological deficits such as hemiparesis (about 1.1% to 16% of patients) (79-85).

1.4.2 Risks Identified for this Study

- Excessive bleeding, fainting or feeling lightheaded, hematoma, or infection may result from having blood drawn (approximately 20cc) for pre-surgical screening. The expected frequency of these complications is rare. Blood will be drawn for pre-surgical screening in a clinical care environment, by fully trained phlebotomist, and with appropriate resources and equipment on hand to handle any complications which may arise during the procedure. The site from which blood is drawn will be thoroughly disinfected prior to the procedure, and protected afterward with antibiotic cream and bandage.

- Risk of temporary sensations of warmth or localized heating during the pre and post-surgical MRIs. The expected frequency of these complications is rare. MRI is generally accepted as a procedure which has no harmful effects on biologic tissue (86). Most complications associated with MRI have occurred because proper procedures (e.g., screening for metal objects) were not followed. MRIs will be obtained in a clinical care environment, by trained radiology technicians, and with appropriate resources and equipment on hand to provide immediate medical assistance for any discomfort or complications which may occur.

- Risks due to anesthesia, including aspiration, coughing, gagging, muscle spasms in the voice box, laryngospasm, bronchospasm, hypertension, tachycardia, damage to teeth and lips, swelling in the larynx, sore throat, hoarseness, heart attack, stroke, awareness during anesthesia, as well as unanticipated allergic reaction, and possibly death. The expected frequency of these complications is low. Anesthesia will be performed by a trained and board-certified anesthesiologist in the controlled medical environment of the operating suite. The subject's vital signs will be closely monitored during the entire procedure to watch for signs of complications due to anesthesia. The appropriate equipment and personnel will be available in the operating room to respond to any complications due to anesthesia.

- Intracranial hemorrhage, subdural hematoma, or epidural hematoma could result in headache, seizures, stroke, temporary or permanent neurologic impairment such as weakness, sensory loss, or coma, change in consciousness, or death. The expected frequency of these complications is low: reports of neurosurgeries for the treatment of epilepsy or implantation of deep brain stimulators suggest that the incidence of bleeding may be between 0.8% and 3.9% (79-85, 87-90). The surgery will be performed by trained and board-certified neurosurgeons in a controlled medical environment. Major blood vessels will be avoided when the NeuroPort Array is implanted. The subject's vital signs will be closely monitored during the entire procedures to watch for signs of surgical complications. The appropriate equipment and personnel will be available in the operating room to respond to any complications due to anesthesia. The

surgery will be performed according to the surgical manual included in the 510(k) application for the NeuroPort Array. During the first two days of post-operative recovery period at USC the patient will undergo a CT scan to ensure that there is no bleeding from the device implantation procedure. The patients will be placed on Keppra 500 mg PO q12 hours for two weeks for routine seizure prophylaxis.

- Cerebrospinal Fluid (CSF) leakage during the surgery could result in a dull or throbbing headache or need for additional surgery, and could be a factor for increased risk of infection. The expected frequency of these complications is low. Evidence from the literature suggests that CSF leakage occurs in a low percentage of neurosurgeries: in epilepsy-related procedures, for example, the incidence of CSF leakage has been reported from 0.1% to 1.4% (88, 89). CSF leakage has been implicated as a potential factor for increased risk of infection (74). Subjects will be monitored closely intraoperatively and during post-operative critical care and throughout the study to watch for signs of CSF leakage. The attending physician will medicate pain as determined medically necessary, and will determine the appropriate response if medication is insufficient.

- Infection could occur after surgery, including meningitis (which has the potential to cause brain damage or hearing loss). The expected frequency of these complications is low: the rate of infection in similar neurosurgeries suggests that the rate of infection in this study may fall between 1.7% and 9.1%, with most reports from the last decade within the range 1.7% to 4% (79-85, 87-90). After the implantation surgery, the subject will receive critical care for a minimum of 1-2 days in the hospital. The patient will receive 24 hours of IV antibiotics post-op. During this time, the subject will be closely monitored for any signs of systemic infection and infection around the wound. If any infection occurs, the subject will receive immediate, appropriate clinical treatment.

- Short-term pain in the head or neck might occur after surgery. The expected frequency of these complications is moderate. The subject will likely experience discomfort in the head and neck due to the nature of the surgery. This pain will be short-term, and should dissipate during the post-operative critical care period, or during the healing period. The attending physician will review each subject's condition individually to determine whether the discomfort requires pharmacological intervention or other response.

- Allergic reaction to the implanted devices is possible. The expected frequency of this complication is low. The NeuroPort Arrays are manufactured using biologically-safe materials, and have a documented history of being implanted both acutely and chronically without incidence of allergic reaction. The NeuroPort Arrays are cleared under 510(k) approval for implantations of less than 30 days. Subjects will be monitored closely during surgery, during the post-operative critical care period, and throughout the study to watch for signs of allergic reaction to the implanted device. If symptoms occur, they will be evaluated by the attending physician, who will determine the proper response (ranging from medication to explantation and exit from the study).

- Discomfort or lack of healing of the skin area could occur at or around the site of the implanted percutaneous connector. The expected frequency of occurrence for this complication is moderate. In studies of bone-anchored hearing aids, severe skin irritation or infection has been reported in 1.0% to 5.0% of all observations (68-70). However, low-to-moderate skin irritation or infection (i.e., treatable via medication) has a higher rate of incidence – 5.1% to 14.0% (68, 71). The wound site will be carefully monitored at all stages of the study, and the subject questioned, to detect signs of discomfort or inadequate healing. Such symptoms and conditions will be treated appropriately and immediately at the direction of the attending physician.

- Tissue damage and histological responses could lead to functional deficits and increased long-term risk of neurological disorder. The expected frequency of these complications is low. When subdural electrode strips are placed to localize epileptogenic tissue, transient neurological deficits have been reported in 5.6% to 11.1% of cases (87, 89). For tissue resection, rates of transient neurologic deficit increase to 8.6% to 30% (90, 91). Permanent neurologic deficits due to stereotactic electrode placement are rare, reported at 0.6% to 1.5% (85, 87, 91). The NeuroPort Arrays are small (4 mm x 4 mm) and short (electrodes are 1.5 mm in length), and will displace or damage small amounts of tissue. During the study, the subject will be monitored on a daily basis by caregivers, and evaluated regularly by physicians, to watch for seizures, loss of function, change in function or behavior, or any other signs of complications. If any appearing symptoms are specified as exit criteria, the patient will be explanted and exit the study.

Otherwise, the attending physician will judge whether conditions are serious enough to warrant explantation.

- Chronic risk of infection associated with the implanted device. The expected frequency of this complication is low. In studies of bone-anchored hearing aids, severe skin irritation or infection has been reported in 1.0% to 5.0% of all observations (68-70). However, low-to-moderate skin irritation or infection (i.e., treatable via medication) has a higher rate of incidence – 5.1% to 14.0% (68, 71). Wound care will be performed regularly and will be monitored on a daily basis by the caregiver, and evaluated regularly by a physician. Excess redness, swelling, drainage, inflammation, or bleeding will be reported to the physician for appropriate urgent follow up care. If the subject experiences any allergic reaction to wound cleaning materials, appropriate substitutes will be found. During the course of the study any infections deemed minor or superficial in nature by the attending physician will be treated and monitored. An infection deemed serious in nature by the attending physician is a withdrawal criterion for the study (Section 4.2.4) and would result in immediate explantation and treatment of the infection.

- The subject will be conducting tasks involving electrical and/or mechanical equipment which could harm the subject. The expected frequency of this complication is low. End effectors, whether physical or virtual, will be electrically and mechanically isolated from the patient so that no physical or electrical harm to the subject could result from use of the effector. The NeuroPort Biopotential Signal Processor receives data from the NeuroPort Array via an optically isolated amplifier. Thus, electrical phenomena have no path from an end effector, physical or virtual, back to the NeuroPort Array. In the case of the physical effector, the physical device would be placed sufficiently distant from the subject so that no contact is possible during task behavior or otherwise. Additionally, an emergency stop button would be available to the operating technician which will immediately remove power from the physical effector.

- The subject could experience frustration while trying to learn brain control in the study sessions. The expected frequency of this complication is low. We intend to select a subject who is mentally and emotionally able to participate despite the rigors of participation. Subject inclusion/exclusion criteria include: stable psychosocial support system, sufficient decision-making capacity, memory, and intellectual capabilities, and no evidence of psychotic illness or chronic psychiatric disorders. The subject will be monitored for signs of severe stress, fatigue, or frustration. The difficulty and frequency of study tasks will be adjusted if any of these signs are observed.

- Electrostatic discharge (ESD) from electrical contacts in the percutaneous pedestal connector presents a risk to the subject. The expected frequency of this complication is low. Electrode contacts in the percutaneous connector are electrically isolated from other metal components of the percutaneous connector and only ESD through the electrode contacts constitutes a concern; any discharges into the metal pedestal will dissipate through the skin as normal. The subject will be instructed to the leave the pedestal cap, which protects the electrical contacts, in place. Only study investigators will be allowed to remove the cap for recording during study sessions. Study investigators will be trained in how to properly remove and replace the pedestal cap in order to avoid ESD. The connector on the patient cable is designed to dissipate ESD during mating in order to reduce risks and minimize patient discomfort.

- Headache and pain. The expected frequency of this complication is moderate. Post-operative pain will be managed with pain medications and will be evaluated regularly during post-operative follow up with the physicians. Additionally, the caregiver and study personnel will perform basic monitoring on a more frequent basis and report any symptoms to physicians promptly for proper care.

- Tissue response to the implanted device may cause a reduction in, or complete inability to, record neural signals. The expected frequency of this complication is moderate. The histological response of brain tissue to implanted electrodes is well studied and has been implicated in a reduction in the quality of neural signals recorded over time (52-56, 92). However, the BrainGate and BrainGate clinical studies have demonstrated neural control using a NeuroPort Array after 1,000 days of implantation (7), and other nonclinical studies have demonstrated useful signals from chronic neural implants primates (56, 93-101). These results suggest that even with a reduction in signal quality, the NPS may still be viable as a neural interface.

- The device may stop working on its own. Because the NPS is an electromechanical system, it is possible that some component of the system may break and cause the device to stop working. The device is

manufactured under a quality control system (Blackrock Microsystems), which reduces the chance of the device malfunctioning on its own. Because the NPS comprises two NeuroPort Arrays, if one breaks the other will still be able to provide neural signals. In that situation, the functionality of the NPS may be reduced and the study tasks and outcomes will be adjusted accordingly, but still to address the safety and effectiveness of the device.

1.4.3 Justification for Study

The novelty of this study is that we intend to explore the safety and effectiveness of a long-term, cognitive neural implant. This novelty is manifest in two primary aspects of the study: first, that we will implant NeuroPort Arrays for a period of one year; and second, that we intend to use signals from posterior parietal cortex, which are involved in high-level plans for reaching and grasping. The nature of these signals is such that other benefits may be derived, such as bimanual control, fast learning, fast adaptation, and dexterous manipulation of virtual or physical end effectors. We have structured this study to explore both the safety and the effectiveness of such a device.

The primary risk to subjects in this study is that of infection. A reasonable expectation of the risk of chronic infection may be derived from the literature regarding bone-anchored hearing aids. Similarly to the NPS, these devices use a bone-affixed titanium implant which remains exposed through the skin. Rates of serious infection (i.e., requiring surgical intervention) associated with these similar devices range between 1.0% and 5.0%; rates of low or moderate infection (i.e., treatable extraoperatively) range from 5.1% to 14.0%. While the implants are not exactly the same (e.g., no osseointegration for the NPS), the materials and chronic, through-the-skin nature of the two implants suggests that similar rates of infection might apply to this percutaneous connectors in this study. With procedures in place to carefully monitor for signs of irritation and infection, it is our view that this risk is acceptable in the context of the benefits to be derived from the study.

Other significant risks are associated with anesthesia and surgeries to implant and explant the device. This section has presented data from the literature describing risks and complications from other, similar clinical procedures including deep brain stimulators, neurosurgical treatments for epilepsy, and general neurosurgical data. For example, it is expected that rates of post-operative infection might fall in the range between 1.7% and 4.0%. The subjects in this study will undergo surgery with a highly skilled clinical team, and will be carefully monitored post-operatively with a standard 24-hour course of antibiotics. It is again our view that with proper management of the risk factors by an experienced team of physicians, the risks associated with anesthesia and surgery are acceptable in the context of the benefits of this study.

The safety of the device has been demonstrated extensively in the literature. Several instances of chronic implantations of NeuroPort Arrays exist in the literature for human subjects and CerePort Arrays for nonhuman primate subjects. In one report from the BrainGate trials, performance of a brain-computer interface was evaluated 1000 days after implantation in a person with tetraplegia (7); other reports from that same clinical study have not described any clinical emergencies or trauma resulting from the implantation of the NeuroPort Array or participation in study tasks (1-6, 8). Many studies exist which have evaluated data recorded with NeuroPort Arrays implanted in nonhuman primates (56, 93-101). These examples demonstrate a history of safety of the NeuroPort Array.

The effectiveness of relying on signals from the posterior parietal cortex for neural interface control has also been well established in the literature. The posterior parietal cortex (PPC) forms a juncture between sensory and motor areas and is involved in sensory-motor integration (15-17). A number of studies relying on electrophysiological, neuropsychological, and neuroimaging results have shown that in humans, areas BA5 and AIP are strongly activated during reaching and grasping (37-48). Our lab group has been instrumental in advancing an understanding of the cognitive signals available in the posterior parietal cortex (14, 19, 27, 28, 31, 57, 58, 67, 102-105).

The proposed study will allow us to perform long-term brain-computer interface training, which takes advantage of neuroplasticity to enhance volitional control over neural activity. The information that is learned will provide a basis for the development of fully-implantable brain-computer interfaces that can control complex assistive technologies. Our main long-term goal, to utilize signals from chronic neural recordings to control external assistive devices, is likely to be perceived as a significant benefit by the targeted patient population. Individuals with high cervical spinal lesions consider restoration of hand and arm function to be a top priority for improving their ability to perform activities of daily living independently (106). We believe that the potential benefits for the

targeted patient population, in concert with properly managed risk, amount to a strong justification for pursuing this clinical study.

1.5 Central Hypotheses

We hypothesize the following regarding the safety of the device:

(1) Implantation will not be associated with infection or irritation;
(2) The Severe Adverse Event (SAE) rate, calculated as the number of SAEs per implant-day, will not rise above 1% for any study subjects.

We hypothesize the following regarding the effectiveness of the device:

(1) Control over virtual and physical end effectors, as measured by accuracy, will be significantly greater than chance when using the NPS;
(2) Action Research Arm Test (ARAT) scores will improve over the course of the trial when controlling virtual or physical end effectors
(3) Using the NPS with either virtual or physical end effectors will result in significant increases in the subjects' quality of life.

2.0 Objectives and Purpose

2.1 Primary Safety Objective

The primary objective of this study is to evaluate the safety of the NPS. The driving hypotheses are that the implantation will not be associated with infection or irritation, and that the SAE rate will not rise above 1%. These hypotheses will be evaluated via the endpoints defined in Section 10.1.

2.2 Primary Effectiveness Objective

The primary effectiveness objective of this study is to evaluate the effectiveness of the NPS in controlling virtual or physical end effectors. The driving hypotheses are that control over the physical and virtual end effectors, as measured by accuracy, will be significantly greater than the level of chance; that scores on the ARAT will improve over the course of the study; and, that using the NPS with either the virtual or physical end effector will result in significant increases in the participant's quality of life. These hypotheses will be evaluated via the endpoints defined in Section 10.2.

3.0 Study Design

3.1 Overview

A prospective, longitudinal, single-arm early feasibility study will be used to examine the safety and effectiveness of using the NPS with physical and virtual end effectors. Figure 3-1 illustrates the progression of a subject through the study from recruitment to study exit. Two subjects will be enrolled, each implanted with the NPS for a period of 53 weeks. The study is expected to take two years in total.

At the end of the study period, it is expected that the subject will have the device removed, continue with follow-up care, and end all study-related activities. However, it may be necessary to evaluate a continuation of the study period if the subject expresses a desire to keep the device. The subject, caregiver, clinical team, and research support team will consult to determine whether it is safe and feasible to do so. If the subject and team agree to allow the device to remain implanted, a new informed consent for long-term follow up will be obtained, and the appropriate oversight bodies (i.e., FDA, IRB, and monitoring organization), will be notified.

All surgical and medical care will be provided according to best medical practice, including protocol activities and care provided in an emergent situation.

A schedule indicating the expected time required for each step of the study is listed in Table 3-1. Because the Recruitment phase depends on the availability and qualifications of an as yet unknown person, there is no specific amount of time listed.

Table 3-1. Study time course

Study Week	**Study Phase**	**Section**
N/A	Recruitment	3.2
0	Informed Consent	3.3
0	Eligibility	3.4
1	Baseline/pre-implant	3.5
2	Device implantation	3.6
2 – 3	Healing period	3.7
4 – 53	Study period	3.8
54	Device explantation	3.8.3
54 – 66	Follow-up care	4.0

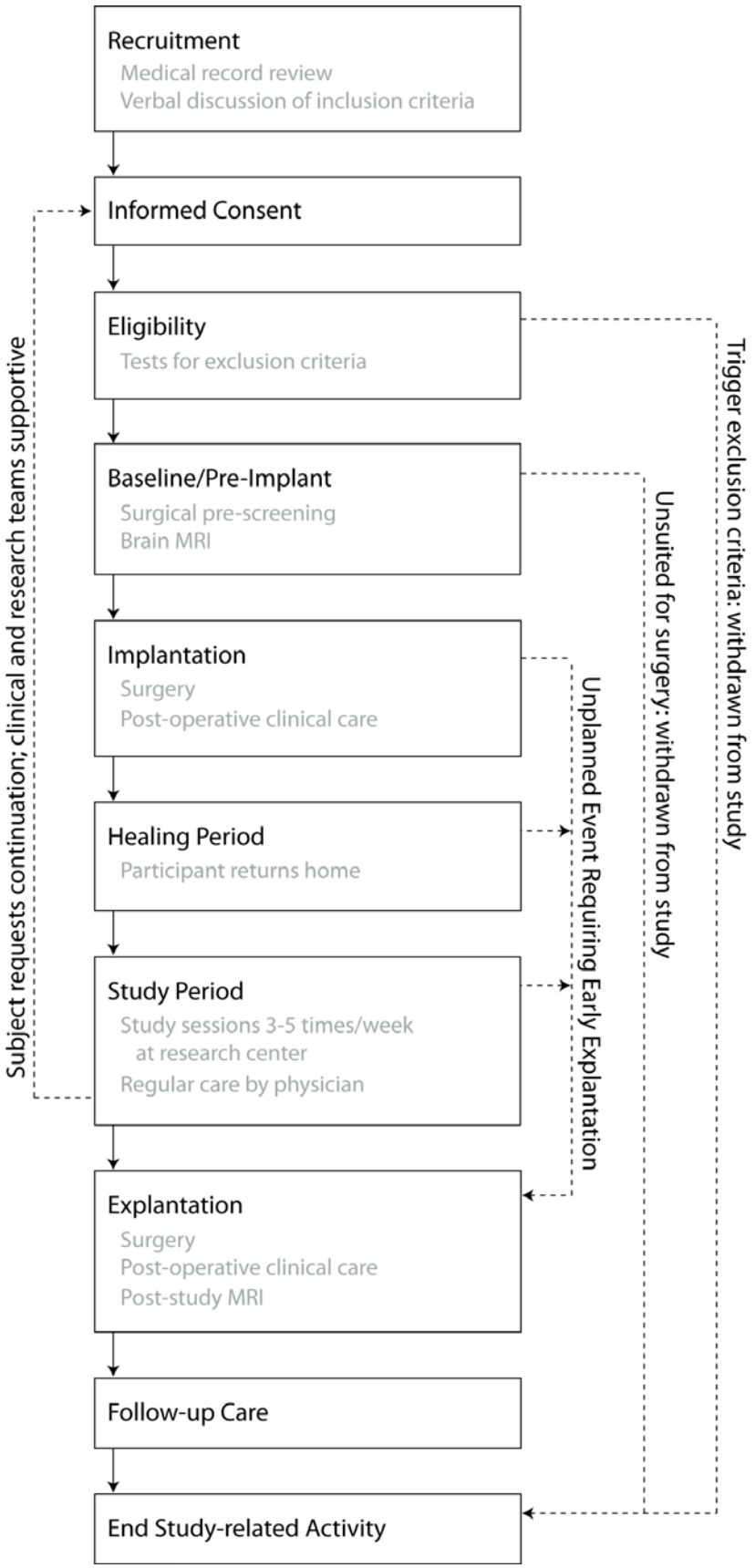

Figure 3-1. Participant progression through the proposed study.

3.2 Recruitment

The search for subjects will be conducted in collaboration with RLANRC. Study applicants will be invited to meet with the clinical investigators, during which the basic elements of the study will be presented and the applicant may ask questions. If the applicant expresses interest in enrolling, then permission will be obtained from the applicant to view their medical records and speak with their primary care physician. The inclusion criteria outlined in Section 5.1 will be evaluated according to the methods defined in Table 5-1. No tests will be performed on the applicant during recruitment. All inclusion criteria will be evaluated via medical record review, consultation with the subject's primary care physician, and interaction with the subject. If the applicant continues to express interest and meets all inclusion criteria to the satisfaction of the study investigators, the applicant may provide informed consent to join the study.

3.3 Informed Consent

Informed consent from study applicants will be obtained by Dr. Charles Liu, M.D., Ph.D., a study co-investigator and neurosurgeon at Keck Hospital, with caregiver(s) present. The informed consent process will include a full description of the risks and benefits of the study to ensure the subjects understand that the NPS is an investigational research device, with limited supporting clinical information. The responsibilities of the caregiver in monitoring and caring for subjects will also be reviewed. Once the applicant has provided informed consent to participate in the study, he or she will be classified as an enrolled study subject and will move to the eligibility phase.

Subjects may withdraw from the study at any time after enrollment at their own request, at the request of the attending physician, due to adverse events or effects, or due to medical conditions which may not be associated with the device (Section 5.3).

3.4 Eligibility

After informed consent has been obtained, the subject will be evaluated against the study exclusion criteria as outlined in Section 5.2. This phase of the study involves some tests whose only purpose is study-related, including the Rey Auditory Verbal Learning Test, Cognitive Abilities Screening Instrument, Symptom Checklist-90-Revised Test, eye exam, urine pregnancy test (if applicable), and physical examination. With the exception of criteria determined by these tests, exclusion criteria will be evaluated via medical record review, consultation with the subject's primary care physician, and survey of the subject (i.e., verbal interaction). If any of these criteria are triggered during the eligibility phase, the subject will be withdrawn from the study and will end all study-related activities. Otherwise, if the subject passes all exclusion criteria to the satisfaction of the study investigators, the subject may continue to the baseline/pre-implant screening phase.

3.5 Baseline/Pre-Implant

Once the subject has been declared eligible to receive the device, a complete medical baseline will be generated. This assessment will include a complete medical history, physical examination, complete neurologic exam, vital sign measurements, blood samples taken for clinical laboratory tests, and EKG. The baseline measurements will serve to provide a standard against which to monitor the health and wellbeing of the subject throughout the study.

After the baseline measurements have been finalized, surgery for device implantation will be scheduled. Within 7 days of the surgical procedure, standard pre-implant procedures will be performed, including a chest X-ray and the usual preoperative blood tests (CBC, CMP, AA Chem, UA, RPR, and PT/PTT; for women of childbearing potential, a urine pregnancy test). A pre-surgical MRI will be obtained to prepare for stereotaxic coordination of the implantation.

3.6 Implantation

Two NeuroPort Arrays will be provided by Blackrock Microsystems (Salt Lake City, UT). Each device will be sterilized prior to delivery, and will be delivered in a sterile chevron pouch. Device implantation procedures are detailed in the NeuroPort Array surgical manual and are briefly described here.

Pre-surgical MRI images will be used for surgical targeting. At the beginning of surgery, the subject will be placed under general anesthesia and a CRW stereotactic frame will be attached to the skull using four pins. Preoperative

antibiotics (Vancomycin 1 gram IV) will be administered and the CRW frame will be secured to the operating table with a Mayfield clamp. The Radionics stereotactic hardware will be calibrated to the stereotactic coordinates obtained from the MRI, corresponding to the posterior parietal cortex. The subject's scalp will be shaved around the area of the craniotomy, prepped and draped over the implantation areas. One scalp incision will be made to prepare for a single craniotomy over the parietal region, approximately two inches in diameter, providing access to both BA5 and AIP.

The first NeuroPort Array will be removed from its packaging and the pedestal screwed to the contralateral skull with eight titanium bone screws. The pedestal will be placed away from the craniotomy, contralaterally, toward the midline, either slightly anteriorly or posteriorly as indicated by the array placement, and placed so as to provide both a safe location and limit discomfort for the subject when the subject's head is supported (e.g., pillow or chair headrest). Following attachment of the pneumatic inserter to the stereotaxic frame, the dura over somatosensory cortex will be opened with a scalpel in preparation for array implantation. The array will be placed on the cortex with the cable orientated in a neutral position so as not to exert force on the array. The pneumatic inserter will be aligned over the back of the array. The inserter wand will be lowered so that it contacts the NeuroPort Array at the peak of cortical pulsations caused by respiration and heart beats. At the point when the NeuroPort Array reaches its highest point the trigger for the pneumatic inserter will be pressed to insert the array into the cortex.

After the first NeuroPort Array is secured, the procedure will be repeated to secure the second pedestal to the contralateral skull, and place the second array through the existing craniotomy. The second pedestal will also be placed contralaterally to the craniotomy, toward the midline, with enough space between the two pedestals to connect both patient cables simultaneously, and with considerations of safety and comfort. Following the second array insertion, the inserter will be removed from the stereotaxic frame.

A duraplasty with Duragen will be performed at the craniotomy to protect the arrays and the cortex. Titanium mesh will be used for a cranioplasty and secured to the skull with titanium screws. The scalp around the pedestals will be closed with nylon sutures and dressed with antibacterial ointment. The CRW frame will then be removed. In total, the surgery is expected to last approximately 2 to 5 hours.

After surgery, a protective cap, provided with the array and pedestal, will be screwed onto the threaded head of the pedestal to protect the electrical contacts. The cap will be unscrewed at the beginning of the study sessions by trained operators to allow for connection of the patient cable and then replaced at the end of each study session. The cap will not be removed otherwise, except as necessary for clinical care, and only by trained study personnel except in emergencies.

While the subject is recovering from surgery, study personnel will visit with the subject and caregiver to review procedures for care of the wound site.

The subject will be transferred post-operatively to the intensive care unit where they will be kept under observation for 2 days or until deemed stable for transfer. The subject will receive 24 hours of post-operative IV antibiotics. The subject will undergo a CT scan to ensure that there is no intracranial bleeding. Subsequently, they will be transferred to the RLANRC acute care unit for 2 days, for further recovery from surgery. During this critical post-operative recovery period, at both Keck Hospital and RLANRC, the subject will be seen twice a day by neurosurgeons. Following this critical care period the subject will be allowed to return home. The subject will have follow-up visits for clinical care at one week, six weeks, and three months after surgery to monitor the healing process.

While the subject has the NPS implant, several procedures will be contraindicated (as specified in the surgical manual for the NeuroPort Array: MRI, electrosurgical cautery, diathermy, peripheral nerve stimulation, transcranial magnetic stimulation, lithotripsy, radiation therapy, therapeutic ultrasound, and defibrillation. Other medical procedures such as dental work, electrolysis, or the implant of another medical device in the body may be performed with caution. The subjects will be instructed to confer with the study doctor before considering such procedures. Each subject will wear an alert bracelet indicating these precautions.

3.7 Healing Period

Following the in-hospital critical care period, the subject will be released to return home. Wounds will be monitored on a weekly basis. Wound care instructions will be provided to the patients and their caregivers. The healing period will last 2 weeks, during which the subject will receive no less than two follow up visits with the

neurosurgeon and neurologist while the wound site heals. During this period, the NPS may be tested briefly for functionality, but no study sessions will occur.

3.8 Study Period

During the study period, study sessions will occur 3-5 times per week at RLA or the subject's residence. Study sessions will provide subjects the opportunity to practice using the NPS to control virtual or physical end effectors in a variety of tasks. Subjects will continue to receive regular clinical follow-up care by the attending physician, to occur not less than monthly for the initial three months then every two months.

During study sessions, subjects will be instructed to use motor imagery to perform variations of two basic tasks involving either physical or virtual end effectors. Task 1 (Section 3.8.1) involves goal-oriented reaching and/or grasping to discrete targets at fixed locations in space, while Task 2 (Section 3.8.2) involves continuously variable movements. Both tasks can be performed in a virtual environment or with a physical end effector, such as a robotic arm (Section 3.8.3).

For each of the two tasks, various imagination and visual presentation methods will be tried to determine the method providing the greatest accuracy. For instance, the subject may obtain the most accurate control when imagining a hand pointed toward the target location; alternatively, the subject may obtain higher accuracy when imagining arm movement. In the case of visual presentation, seeing a physical robot arm moving toward a physical target location instead of a virtual robot arm moving toward a virtual target might lead to enhanced control.

The accuracy with which subjects complete tasks under conditions like these will serve as the primary endpoint for measuring effectiveness, and will be compared against chance. Additionally, the standardized Arm Research Action Test (ARAT) will be administered and scored by Occupational Therapists at RLANRC as a secondary endpoint for measuring effectiveness. It is expected that performance in the standardized ARAT will serve as a guide to understanding how to gauge the significance of the primary accuracy endpoint, and may additionally allow some comparison with other methods of intervention. Finally, subjects will verbally complete a quality-of-life survey, validated for the paralyzed population, as a third endpoint monitoring effectiveness.

3.8.1 Task 1 – Fixed Targets

In the training phase of Task 1, a target object will be presented at one of a number of fixed locations in either virtual or physical space. In virtual space, the target object would be virtually displayed in a 3-dimensional image on a computer screen. In physical space, a target object would be placed in the subject's field of view. The subject will be instructed to imagine either reaching to the target and/or grasping the target, the latter requiring different imagined hand configurations. The neural activity associated with each location will be recorded by the NPS computer apparatus and used to construct a database. After sufficient training data has been collected, the assessment phase will begin. Experimental work with nonhuman primates has shown that acquiring such training data requires 5-20 minutes per study session.

On each trial of the assessment phase, a target object will be presented at one of the fixed locations in virtual or physical space, and the subject will again be instructed to imagine reaching and/or grasping the target. The NPS apparatus will analyze up to one second of neural activity following each target presentation. It will then decode the neural activity using information in the database and read out the imagined, intended target location and/or hand configuration. The decoded location and/or configuration will be translated into movement of a virtual or physical end effector. A virtual effector could be a 3-dimensional representation of a robotic arm, which moves and interacts in the virtual space in which the target is presented. A physical effector could be a robotic arm, which would be positioned within the subject's field of view but at least 4 feet distant from the subject. In both settings, the subject will have constant visual feedback about the success of the decoding algorithm and about the deviation between what was imagined and what the algorithm is able to decode. In addition, auditory feedback cues will indicate success or failure.

3.8.2 Task 2 – Continuous Positioning

In the training phase of Task 2, the subject will be asked not only to imagine the goal of a movement but also the continuous transfer from the start location or initial hand configuration to the target location or hand configuration. Such tasks will include tracing (by imagined arm and hand movements) the trajectory of a physical or virtual

robotic hand moving to a target location; or, to imagine mimicking the fine movements of a physical or virtual hand closing around or manipulating an object. Neural activity during these time frames will be recorded and used to construct a database. After sufficient training data has been collected, the assessment phase will begin. Again, this training data collection is estimated to take 5-20 minutes per session.

On each trial of the assessment phase a physical or virtual effector will be presented in a starting configuration and the subject will be instructed to imagine the motor process to control the effector's trajectory to acquire a target location or hand configuration. Neural activity recorded during each trial will be compared to the database in near real-time and used to update the predicted location and shape of the hand.

3.8.3 End Effector

Study subjects will use the Modular Prosthetic Limb (MPL), a robotic arm designed through the Johns Hopkins University (JHU) Applied Physics Laboratory (APL). The MPL has 17 degrees of freedom, and, fully extended, the MPL is 790.7 mm (just over 2'7") long. It was designed to approximate the function of a human arm, and its ranges of motion were specified to match those of a human arm as closely as possible.

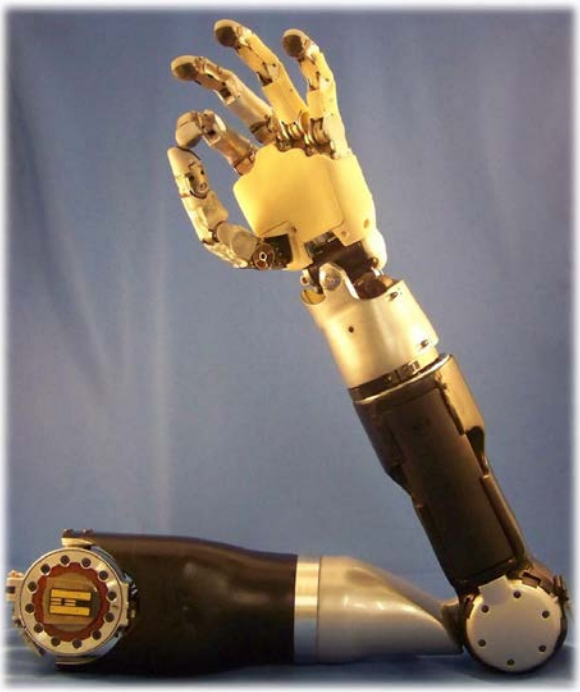

Figure 3-2. The JHU/APL Modular Prosthetic Limb (MPL).

The MPL will be bolted to a steel frame at least four feet from the subjects, such that it will not be possible for the MPL to physically interact with a subject during a task. When a task is not active, the MPL will be powered off, or fixed in position by software and unable to move. The MPL will be controlled via computer. There will be no physical or electrical feedback pathways from the MPL back to the subject. The subject will use only visual feedback to monitor operation of the limb.

Because there will be no physical, electrical, or other interaction between the subject and the MPL (except for visual observation), there is no context in which the safety of the Neural Prosthetic System (NPS) is affected by the presence of the MPL as an end effector. The MPL is a modular substitute for a virtual environment and represents no additional risk or need for additional safety assessment.

A computerized, three-dimensional model of the MPL is available as a virtual end effector for the NPS. The components of physical tasks, such as blocks, balls, shelves, washers, etc., will be replicated in the virtual environment so that the tasks can be administered in both the virtual and the physical environments. Alternatively, a computer cursor could be used as a virtual end effector for simple tasks.

3.9 Explantation

Explantation could occur earlier than at the conclusion of the study period if withdrawal criteria are met (Section 5.3). In such a case, the NPS would be explanted unless clinical or ethical concerns determined by the sponsor-investigator and clinical team mandate otherwise.

In the default (and expected) case, the NPS implant will be explanted at the conclusion of the study period. In the event of explantation, the subject will be returned to the operating room where peri-operative antibiotics will be administered. At the beginning of surgery, the subject will be placed under general anesthesia and a CRW stereotactic frame will be attached to the skull using four pins. Preoperative antibiotics (Vancomycin 1 gram IV) will be administered and the CRW frame will be secured to the operating table with a Mayfield clamp. The scalp will be shaved, prepped, and draped over the incision site and the pedestals. The incision will be re-created initially over the craniotomy sites, and the scalp will be elevated over the titanium mesh. Bacterial cultures will be obtained if found to be necessary by the attending neurosurgeon. The screws securing the mesh and the titanium mesh itself will be removed. A plane of dissection under the dura and Duragen will be established. The electrode arrays will be removed by hand from the cortex. This portion of the wound will be irrigated with antibiotic flush, and a new piece of Duragen will be placed over the defect in the dura. A new titanium mesh will be used for a cranioplasty and secured to the skull with titanium screws. All plates securing the array cables leading to the pedestal will be removed, and the electrode arrays will be cut from their cables and saved for analysis. The incision over the craniotomy will then be closed with 3-0 nylon sutures. An incision will then be made around the pedestal. Bacterial cultures will again be obtained, if found to be necessary by the attending neurosurgeon. The pedestal screws and the pedestal, along with the attached cables will be removed. The wound edges around the pedestal will be debrided to viable tissue. This portion of the wound will also be irrigated with antibiotic flush and closed with 3-0 nylon suture. Both wounds will be dressed with antibiotic ointment and sterile gauze, and the Mayfield holder will be removed.

The subject will be transferred post-operatively to the intensive care unit where they will be kept under observation for 2 days. The subject will undergo a CT scan to ensure that there is no intracranial bleeding. The subject will also receive a final MRI for comparison with the pre-implant MRI. Subsequently, the subject will be transferred to the RLANRC acute care unit for 2 days, for further recovery from surgery. During this critical post-operative recovery period, at both Keck Hospital and RLANRC, the subject will be seen twice a day by neurosurgeons. Following this critical care period the subject will be allowed to return home.

3.10 Follow-up Care

After being discharged from the hospital, the subject will return home. The subject will have follow-up visits for clinical care at one week, six weeks, and three months after surgery to monitor the healing process. The subject's experience in the study will be evaluated by a questionnaire which will assess health, safety, adaptation, and capabilities of the NPS.

4.0 Device Information

4.1 Device Overview

The Neural Prosthetic System (NPS) is a medical device implanted into the parietal cortex for the purpose of providing severely paralyzed individuals novel capabilities for interacting with an environment. The NPS comprises two NeuroPort Arrays.

4.2 IDE Number

The IDE number of the NPS is G120096.

4.3 NeuroPort Array

The NeuroPort Array is manufactured by Blackrock Microsystems, Salt Lake City, UT, USA.

NeuroPort Arrays allow for the local recording of cerebral cortex. Key features include sterile, single use electrodes that provide access to a localized population of individual cells. The main component of the NeuroPort Array is an array comprised of 100 microelectrodes (1.5 mm in length) uniformly organized on a 4 mm x 4 mm silicon base that is 0.25 mm thick. Each microelectrode is insulated with Parylene-C polymer and is electrically isolated from neighboring electrodes by non-conducting glass. Each microelectrode has a platinum tip that is 100-200 microns in length and offers impedance values from 100–800 kilo-ohms. Of the 100 electrodes, 96 are wire bonded using 25 μm gold alloy insulated wires collectively sealed with a silicone elastomer. The wire bundle is potted to a printed circuit board with epoxy, the printed circuit board is inserted into the Patient Pedestal (percutaneous connector), and then the Patient Pedestal is filled with silicone elastomer. Two fine platinum reference wires are also attached to the Patient Pedestal. The Patient Pedestal is 19 mm wide at the skin interface.

Currently, the NeuroPort Array is cleared for temporary (<30 days) recording and monitoring of brain electrical activity. For this study, two NeuroPort Arrays will be used for long-term (53 weeks) passive recording of cortical activity.

Two other components will be used in support of the NeuroPort Array: the Array Inserter, and the NeuroPort Biopotential Signal Processor: the Array Inserter for the NeuroPort Array (Section 4.3.1), and the NeuroPort Biopotential Signal Processor (Section 4.3.2).

4.3.1 Array Inserter for the NeuroPort Array

The Array Inserter is manufactured by Blackrock Microsystems, Salt Lake City, UT, USA.

The array inserter allows for the rapid insertion of a surface aligned array into cerebral cortex. Key features include: a multiple-use trigger-actuated pneumatic piston, and a pressure source. Piston stroke length can be adjusted, which prevents excessive dimpling of cortical tissues upon insertion. Piston actuation is achieved through an actuated chamber that is pressurized with a 120 VAC driven pump. The power source is patient isolated with a hospital grade isolation transformer. This inserter is part of the 510(k) cleared device, the NeuroPort Array.

4.3.2 NeuroPort Biopotential Signal Processor

The NeuroPort Biopotential Signal Processor is manufactured by Blackrock Microsystems, Salt Lake City, UT, USA.

Neural signals read out by the passive implant device are recorded via the NeuroPort Biopotential Signal Processor. The NeuroPort Biopotential Signal Processor allows for the recording of up to 128 channels of activity. Key features include: an optically isolated amplifier capable of recording 128 channels at 30 kHz with 16-bit resolution.

The power source is 120 VAC through a hospital grade isolation transformer. The NeuroPort Biopotential Signal Processor complies with the relevant safety standards for intra-operative and hospital monitoring settings: IEC 60601-2-26, IEC 60601-1-2, UL 2601-1, CAN/CSA-C22.2 no. 601.1-M90.

The NeuroPort Biopotential Signal Processor has received 510(k) clearance for use. It will not be modified in any way from its original 510(k) clearance for use.

5.0 Selection and Withdrawal of Subjects

5.1 Inclusion Criteria

Table 5-1 outlines the inclusion criteria which will be applied to study applicants, as well as the method of evaluating each criterion and the threshold for each criterion. The methods used to evaluate inclusion criteria consist of verbal discussion, medical record review, and consultation with the subject's primary care physician.

Table 5-1. Inclusion criteria, methods of evaluation, and thresholds for inclusion.

Criterion	Method of Evaluation	Threshold
High cervical spinal lesion	Medical Records	History of spinal lesion (C4 and above), with 0/5 distal arm muscle strength in both arms: C5 – Deltoid and biceps C6 – Wrist extensors C7 – Triceps C8 – Finger flexors T1 – Finger abductors Occurred at least one year prior to enrollment Stable for three months prior to enrollment (no signs of improvement)
Age	Medical Records	18-65 years
Provide informed consent	Consultation with Physician	Must be willing and able
Understand and comply with instructions in English	Consultation with Physician	Must be able
Communicate via speech	Consultation with Physician	Must be able
Surgical clearance	Consultation with Physician	Must be cleared
Life expectancy	Consultation with Physician	Greater than 12 months
Travel up to 60 miles to study locations up to five days per week for the duration of the study	Verbal discussion	Must be willing and able
Caregiver monitor for surgical site complications and behavioral changes on a daily basis	Verbal discussion	Caregiver must be willing and able
Psychosocial support system	Verbal discussion	Must be present and stable

5.2 Exclusion Criteria

Table 5-2 outlines the exclusion criteria which will be applied to study subjects, as well as the method of evaluating each criterion and the threshold for each criterion. The methods used to evaluate exclusion criteria consist of some tests (as specified in Table 5-2), survey (i.e., verbal and written interaction with patient), medical record review, consultation with the subject's primary care physician, and physical examination.

Table 5-2. Exclusion criteria, methods of evaluation, and thresholds for exclusion.

Criterion	Method of Evaluation	Threshold
Presence of memory problems	Rey Auditory Verbal Learning Test	Age-dependent (Appendix, section 18.5)
Intellectual impairment	Cognitive Abilities Screening Instrument (CASI)	Score of 26 or less
Psychotic illness or chronic psychiatric disorder, including major depression if untreated	Symptom Checklist-90-Revised Test	diagnosis of Axis I or Axis II
Poor visual acuity	Snellen chart	20/30 or lower
Pregnancy	Urine Pregnancy Test	Positive (Pregnant)

Active infection or unexplained fever	Physical Examination	Evidence of either
Scalp lesions or skin breakdown	Physical Examination	Evidence of either
HIV or AIDS infection	Medical Records, blood work	Positive (infected)
Active cancer or chemotherapy	Medical Records	History of cancer in past 12 months, or evidence of need for chemotherapy during study
Diabetes	Medical Records, blood work	Any
Autonomic dysreflexia	Medical Records	History in past 3 months
History of seizure	Medical Records	Any
Implanted hydrocephalus shunt	Medical Records	Any
Previous neurosurgical history affecting parietal lobe function	Medical Records	Any
Medical conditions contraindicating surgery and chronic implantation of a medical device	Medical Records	osteomyelitis, diabetes, hepatitis, any autoimmune disease/disorder, epilepsy or history of seizures of any kind, skin disorders causing excessive skin sloughing or poor wound healing, blood or cardiac disorder requiring chronic anti-coagulation
Prior cranioplasty	Medical Records	Any
Unable to undergo MRI or anticipated need for MRI during study	Medical Records, Consultation with Physician	Any
Nursing an infant or unwilling to bottle-feed infant	Medical Records, Survey	Any
Chronic oral or intravenous use of steroids or immunosuppressive therapy	Medical Records, Survey	Any
Suicidal ideation	Medical Records, Survey	History in past 12 months
Drug or alcohol dependence	Survey	History in past 12 months
Planning to become pregnant, or unwilling to use adequate birth control	Survey	Any plan for pregnancy, or unwilling to use birth control

5.3 Withdrawal Criteria

Withdrawal is premature conclusion, which may occur at any time. Withdrawal is discouraged, but is a right of the subject. If the subject withdraws, he or she cannot continue to use the NPS. The clinical team and sponsor-investigator will determine whether to explant the device based on clinical and ethical considerations and the nature of the withdrawal. If the subject withdraws and has all devices explanted, there is no need for further physician monitoring of the device, and the patient will receive the standard clinical follow-up care (follow-up visits at one week, six weeks, and three months post-surgery).

The withdrawal criteria are:

- Patient request
- Attending physician (neurosurgeon, neurologist) request
- Serious infection around the percutaneous connector
- 53 weeks of implantation, unless patient opts to retain device
- Pregnancy
- Onset of epilepsy
- Significant change in neurological exam
- Development of serious adverse events, physical or psychological, including negative behavioral symptoms, major depression, or suicidal ideation
- Intracranial infection unresponsive to antibiotic treatment
- Development of intracranial hematoma requiring evacuation
- Need for urgent MRI of any kind (brain or body)

6.0 Stratification/Descriptive Factors/Randomization Scheme

Because this study is structured to evaluate the feasibility of the NPS, there are no elements of stratification or randomization involved in subject selection or device administration. Subjects will be selected who display symptoms characteristic of high (C4) spinal lesion. Each of these subjects will receive the same device, and will participate in the same tasks to evaluate the effectiveness of the device. The health of each subject, including the area around the implant, will be evaluated in the same way for both subjects.

7.0 Study Agent Administration or Intervention and Toxicity Management Plan

7.1 Device Administration

Each subject in this study will receive the same device. The device consists of two NeuroPort Arrays implanted in the posterior parietal cortex. One array will be implanted in Brodmann's area 5, and the second array will be implanted in the anterior intraparietal area. Each subject will undergo the same evaluations to monitor the safety of the implanted device. Each subject will participate in the same set of tasks designed to evaluate the effectiveness of the device.

7.2 Intervention Plan

There are no alternative therapies available for this device, and the condition which predicates this device (paralysis) is not acutely life-threatening, so a slow treatment or absence of treatment does not constitute undue risk to the subject requiring intervention. However, the presence of the device does present increased risk to the subject, particularly in terms of the risk of infection. Thus, it may be determined by the study sponsor that the device cannot be made to work without significant surgical revision or other risk-laden procedure; and, if it is so determined, the study sponsor and co-investigators may opt at their discretion to withdraw the subject from the study as a means of intervention to cease ongoing study-related risk.

7.3 Toxicity Mangement Plan

The NeuroPort Arrays are approved by the FDA to be in prolonged contact with CSF, bone/blood and tissue, i.e., for 30 days or less. (For the purposes of this study, an investigational device exemption has been obtained which approves permanent contact with CSF, bone/blood and tissue). Additionally, the NeuroPort Arrays are constructed using materials with a history of biocompatibility, such as titanium. In order to obtain 510(k) approval for prolonged contact, the NeuroPort Array was required to undergo a suite of tests determining its biocompatibility; the device was determined to be biocompatible for its originally intended use. Furthermore, an extensive body of literature reviewing the CerePort Array in animals and, and a smaller body of work reviewing results of the BrainGate clinical study sequence, have collectively demonstrated no chronic toxicity (see Section 1.3.1 for a review of this evidence). The sponsor and investigators of this study take the evidence at hand to support the view that the device is not toxic. Therefore, this study does not include any toxicity management strategies.

8.0 Assessment of Effectiveness and Safety

8.1 Side Effects Monitoring

8.1.1 Side Effects Monitored During Study

The primary long-term risk associated with the NPS is that of infection. Infection could develop around the percutaneous connectors, or it could develop intracranially. Thus, study subjects will be monitored throughout the study to watch for signs and symptoms of both superficial and intracranial infection.

Monitoring for superficial infection will include participation of the subjects' caregivers as well as study physicians. The caregivers will be trained to observe and maintain the wound site on a daily basis. Physicians will check the wound site monthly over the course of the study.

Monitoring for intracranial infection will also include participation of the subjects' caregivers as well as study physicians. Caregivers will be trained to watch for signs of intracranial infection such as functional deficits and seizure. Physicians will conduct thorough examinations of study subjects, including both physical and neurological, on a monthly basis throughout the study.

8.1.2 Side Effects Monitored After Study

As is routine for patients who undergo brain surgery, the patient will be seen for follow-up visits at one week, six weeks, and three months following the explant surgery. At these visits, the attending physician will execute a full physical and neurological examination to test for any adverse events or effects which may have occurred.

8.2 Adverse Event Reporting

8.2.1 Adverse Event Definitions

Adverse event. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse event may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse event. Any adverse event that places the subject, in the view of the sponsor-investigator, at immediate risk of death from the event as it occurred (i.e., does not include an adverse event that, had it actually occurred in a more severe form, might have caused death).

Serious adverse event. Any adverse event that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

- *Hospitalization* shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse event; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event (e.g., for a preexisting condition not associated with a new adverse event or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse event. Any adverse event, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s), as amended.

Unanticipated adverse device event. Any serious adverse event on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that event, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including a supplementary plan or application),

or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.2.2 Eliciting Adverse Event Information

Clinical study subjects will be routinely questioned about adverse events at study visits.

8.2.3 Recording and Assessing Adverse Events

All observed or volunteered adverse events (serious or mild) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic procedure(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and; 2) an assessment of the causal or potential causal relationship between the adverse event and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse events or abnormal test findings felt to be associated or possibly associated with the investigational device will be classified as serious or mild and will be followed until resolved or stabilized at a level acceptable to the sponsor-investigator.

8.2.4 Abnormal Test Findings

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy. (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.)
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study.
- The test finding is considered an adverse event by the sponsor-investigator.

8.2.5 Causality and Severity Assessment

The sponsor-investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the investigational device or, if applicable, other study treatment or diagnostic procedure(s); and 3) if the adverse event meets the criteria for a *serious adverse event*.

If the sponsor-investigator's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic procedure(s) are deemed necessary", the adverse event will be classified as *associated or possibly associated with the use of the investigational device or study treatment or diagnostic drug procedure(s)* for reporting purposes. If the sponsor-investigator's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic procedure(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

8.2.6 Reporting of Adverse Events to the FDA

The sponsor-investigator will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse event that is determined to be an unanticipated adverse device event. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse event.

If the results of the sponsor-investigator's follow-up evaluation show that an adverse event that was initially determined to not constitute an unanticipated adverse device event does, in fact, meet the requirements for

reporting; the sponsor-investigator will submit a completed FDA Form 3500A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the sponsor-investigator will identify all previously submitted reports that addressed a similar adverse event experience and will provide an analysis of the significance of the newly reported adverse event in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor-investigator will submit additional information concerning the reported adverse event as requested by the FDA.

8.2.7 Reporting of Adverse Events to the Responsible IRB

In accordance with applicable policies of the reviewing Institutional Review Boards (IRBs), the sponsor-investigator will report, to all associated IRBs, any observed or volunteered adverse event that is determined to meet all of the following criteria: 1) *associated with the investigational device or, if applicable, other study treatment or diagnostic product(s);* 2) a *serious adverse event*; and 3) an *unexpected adverse event*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational device or, if applicable, other study treatment or diagnostic product(s);* 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the sponsor-investigator's receipt of the respective information.

Follow-up information to reported adverse events will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the sponsor-investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

8.2.8 List of Adverse Events

The following list comprises adverse events which could occur.

8.2.8.1 CNS: Infection/Vascular/CSF

- CNS hematoma (e.g., subdural, epidural)
- CSF Leakage
- Deep Vein Thrombosis (DVT)
- Encephalitis
- Hemorrhage
- Intracranial hemorrhage
- Meningitis
- Stroke

8.2.8.2 Wound (surgery-related)

- Bleeding
- Drainage
- Edema
- Infection (superficial)
- Irritation
- Soreness
- Pain

8.2.8.3 Pain

- Acute, deep
- Acute, superficial
- Chronic, deep
- Chronic, superficial

- Headache

8.2.8.4 Seizure

- New seizure
- Onset of epilepsy
- Status epilepticus

8.2.8.5 Cognitive Memory

- Attention/concentration difficulty
- Confusion
- Memory difficulty
- Psychomotor slowing/encephalopathy

8.2.8.6 Mood/Psychological

- Agitation/irritability
- Anxiety/nervousness
- Depression
- Emotional liability
- Personality change
- Psychosis

8.2.8.7 Language

- Dysarthria
- Aphasia (e.g., Dysnomia, Dysphasia)

8.2.8.8 Movement/Coordination

- Ataxia
- Coordination difficulties
- Dyskinesia/Dystonia
- Involuntary movements (e.g., twitching, myoclonus, chorea)
- Tremor
- Weakness (paresis)

8.2.8.9 Sensory

- Loss of sensation (e.g., numbness, loss of proprioceptive/vibratory sensation)
- Loss of sight
- Vertigo/dizziness

8.2.8.10 Coma/Death

- Coma
- Death

8.2.8.11 Allergy/Immunologic

- Allergic reaction (e.g., wound care cleaning solution)
- Rejection (e.g., sensor or percutaneous connector)

8.2.8.12 Constitutional/Systemic

- Appetite change
- Edema
- Fatigue
- Fever
- Flu
- Hematologic
- Insomnia/other sleep disorders
- Night sweats
- Weight change

8.2.8.13 Tumor/Cancer

- Cancer, malignant
- Mass/lesion, benign

8.2.9 Withdrawal of Subjects Due to Adverse Events

An adverse event may be serious in nature and require the subject to withdraw from the study. The severity of the adverse event, and whether it constitutes a reason for withdrawal from the study, will be determined by the clinical team and sponsor-investigator. Unless otherwise indicated by the clinical team and sponsor-investigator, the device will be explanted before the subject is withdrawn from the study.

8.3 Data Monitoring Committee

Aptiv Solutions, Inc. (Aptiv) will perform data monitoring over the course of the study.

9.0 Clinical and Laboratory Evaluations and Clinical Calendar

See Appendix, Section 18.1.

10.0 Criteria for Evaluation and Endpoint Definitions

The objectives of this study are to evaluate the safety and effectiveness of the NPS. Each of these objectives will be measured quantitatively as defined in Table 10-1 and described in this section.

Table 10-1. Safety and Effectiveness Endpoints

Objective	Hypothesis	Method of Evaluation	Time of Assessment	Comparisons Made
To evaluate the safety of the NPS implant	Primary endpoint – implantation will not be associated with infection or irritation	Inspection of subject's scalp for evidence of reddening or discharge; review of new symptoms including possible fever, headache, visual or auditory changes, or change in mood or behavior; serial neurologic exams	Immediately after implantation and weekly thereafter	The condition of the area will be compared with its condition on previous visits History will be obtained regarding new symptoms Neurologic exam will be compared to baseline neuro exam
	Secondary endpoint – the Severe Adverse Event (SAE) rate will not rise above 1% for any study subjects.	The SAE rate will be calculated as the number of SAEs per implant-days.	The SAE rate will be available on a daily basis throughout the study.	The SAE rate will be continuously compared to the 1% threshold level.
To evaluate the effectiveness of the NPS	Primary endpoint – patient control over the end effector (virtual or physical), as measured by accuracy, will be significantly greater than chance when using the NPS	Calculated by the NPS computer apparatus	At the end of every study session	Assessments will be compared with chance
	Secondary endpoint – Action Research Arm Test (ARAT) scores will improve over the course of the trial when controlling the virtual or physical robotic arm	ARAT administered by occupational therapists	At 10-week intervals starting at week 3.	Scores will be compared to the baseline, i.e., the first score from week 3.
	Tertiary endpoint – using the NPS with either a virtual or physical end effector will result in significant increases in the subject's quality of life	Quality of Life Inventory (QOLI) administered by the NPS operator	During prescreening (baseline) and every month subsequent to implantation	Monthly QOLI score will be compared against baseline

10.1 Safety Endpoints

10.1.1 Infection and Irritation

Infection and irritation are the most serious risks identified for the NPS, and as such the absence of both serves as a primary safety endpoint for the study. The implant sites will be monitored by visual inspection of the wound margin, verbal survey of the subject, and neurologic exam.

10.1.2 SAE Rate

The severe adverse event (SAE) rate is the secondary safety endpoint. The indicated SAE rate threshold, at 1% SAEs per implant-days, was established based on literature describing adverse events for similar procedures (107, 108).

10.2 Effectiveness Endpoints

Three methods will be used to assess the effectiveness of the NPS while controlling virtual and physical end effectors: comparison of task performance to the level of chance at each study session, standardized tests applied at 10-week intervals, and the Quality-of-Life Inventory (QOLI) applied at 4-week intervals.

10.2.1 Comparison of Task Performance to the Level of Chance

The design of study tasks as described in the original IDE application allows for virtual or physical end effectors. In Task 1 – Discrete Selection, an object will be placed in the subject's field of view and the subject will be instructed to imagine reaching and/or grasping the target object. Each instruction to reach to a target object will be considered the beginning of a trial. If the subject then operates the MPL according to the instructions, the trial will be considered successful; otherwise, the trial will be considered unsuccessful. Then, the percentage of successful trials compared to the level of chance will serve to assess the use of the MPL in the task. In Task 2 – Continuous Positioning, the same method will be used to assess the use of the MPL relative to the level of chance.

10.2.2 Standardized Tests

Two commonly-used, standard tests have been selected by which the use of robotic arm will be evaluated: the Action Research Arm Test (ARAT) and the Canadian Occupational Performance Measure (COPM). These tests will be evaluated at 10-week intervals throughout the study beginning at week 3 (i.e., after the healing period), for a total of six evaluations. The ARAT is widely used in therapy with upper-extremity-disabled populations and may allow for direct comparison with other interventions. The COPM, also widely used, is a subject-centric paradigm designed to measure the subject's perceived performance.

The ARAT (109) was designed to provide a rapid, reliable test to assess recovery of upper limb function following cortical damage. It is composed of four subtests, including grasp, grip, pinch, and gross movement; however, because the gross movement test would require interaction between the robotic arm and the subject, it will not be used. Scoring will be adjusted accordingly, with a four-point scale (0-3) accorded to each of 16 other individual tasks (see ARAT Clinical Note in Section XX). The remaining tasks will evaluate gross through fine hand and arm function.

The COPM (110) was designed to evaluate perceived occupational performance across categories including self-care, productivity and leisure. It is a semi-structured process in which the therapist and subject identify problem areas, the subject rates the importance of each problem, and the subject scores his or her performance in the problem areas. Then, after a period of intervention, performance is re-assessed and a plan for continuation of treatment is formulated. Problem areas applicable for this study could be, for example, grasping or pinching with the extracorporeal device. Scoring is performed on a 10-point scale (0-9) with 0 being "least important" and 9 being "most important."

10.2.3 Quality-of-Life Inventory

The Quality of Life Inventory (QOLI) was designed to incorporate both field-standard quality-of-life measurements as well as study-specific measurements. The QOLI is attached to this supplement as a clinical note in Section XX. In the QOLI clinical note, Section 1 is comprised of questions which are intended to capture NPS-related quality-of-life measurements. These questions were developed specifically for this study, but are potentially relevant for evaluation of other brain-controlled prostheses. Section 2 is the Satisfaction With Life

Scale (SWLS) (111), a standard questionnaire for measuring global life satisfaction. Section 3 is the Subjective Quality of Life (SQOL) (112), a single-item, subjective measure of quality of life. Both the SWLS and SQOL have been validated in populations of paralyzed patients at RLANRC. The SWLS is a standard in the field for measuring global life satisfaction. Thus, the QOLI incorporates both study-specific quality-of-life measurements as well as standard instruments for measuring life satisfaction and quality of life in paralyzed populations.

11.0 Special Instructions

N/A.

12.0 Data Collection and Monitoring

12.1 Case Report Forms

Case Report Forms (CRF) will be used to collect all data from source documents, such as Clinical Notes, Medical Records, and Surveys. Data in CRFs will be verified against data in the source documents and approved (via digital signature) by the sponsor-investigator. CRFs will serve as the official record for the clinical study. CRFs are listed and described in Table 12-1.

Table 12-1. Case report forms.

CRF Name	Source Document
Adverse Event	Clinical Note
Action Research Arm Test (ARAT)	Clinical Note
Canadian Occupational Performance Measure (COPM)	Clinical Note
Conclusion/Withdrawal	Clinical Note
Consent Information	Clinical Note; Informed Consent Document
Inclusion/Exclusion	Clinical Note; Medical Records
Initial Office Appointment	Clinical Note
Office Appointment	Clinical Note
Quality-of-Life Index	Clinical Note
Study Session	Clinical Note
Surgical Procedure	Clinical Note; Medical Records

12.2 Source Documentation and Timeliness of CRF Completion

Source documents are reports or records of medical and health information that are required to be filed in the subject binder or must be made available during monitoring visits or audits. Source documents provide information necessary to complete CRFs. To ensure timely completion, CRFs should be completed within 30 days of contact with the subject.

Clinical Notes are provided to the clinical site. Information recorded in a Clinical Note is transcribed into the corresponding CRF. The person recording the data must sign each page of the Clinical Notes. Any edits must be redlined, initialed, and dated.

The quality of life inventory (QOLI) is provided to the subject to complete during investigation appointments. The inventory itself is the source document. Data is entered into the corresponding CRF.

12.3 Retention of Study Record

Study records will be retained for the duration of the study at a minimum. Thereafter, study records will be maintained for such time as is needed to provide a full report on the results of the clinical study. Medical records will remain with the clinical record on file for the study subject.

12.4 Data Management

CRFs will be collected and stored in a clinical data management system. Each CRF will be uniquely and appropriately named to avoid confusion. Data will be checked for typographical and logical errors, and investigators contacted if clarification is required.

12.5 Data Monitoring

Aptiv Solutions, Inc. (Aptiv) has been contracted to perform data monitoring for this clinical study.

13.0 Statistical Considerations

13.1 Study Objectives

This feasibility study is designed to evaluate the safety and effectiveness of the NPS, a device which records brain activity from the posterior parietal cortex. The safety of the device will be evaluated by monitoring the health of the implant over the course of the study. The effectiveness of the device will be evaluated by monitoring accuracy in certain tasks, as the subjects attempt use their thoughts to control external effectors, and by monitoring the subjects' quality of life, as measured by the quality-of-life index (QOLI) throughout the study. Two subjects will be enrolled in this study. Each subject will serve as his or her own control.

13.2 Accrual

The expected accrual rate for this study is 0.06% (two subjects enrolled out of a population of approximately 3,000 patients seen regularly at RLANRC with some degree of paralysis). The accrual goal is two. Only one site, RLANRC, will be involved in recruiting subjects for this study.

13.3 Study Design

This study is designed as a longitudinal feasibility study in which two subjects will each receive the NPS and each will serve as his or her own control. Each subject may withdraw from the study independently of the other before reaching the end of the study period at his or her request, physician request, or due to an adverse event. If an adverse event occurs which is determined to be caused by a defect of the device, which is determined to place undue risk on the subjects of the study, the study will end early and all enrolled subjects will be withdrawn from the study.

No stratification factors will be incorporated into this study. Both study subjects will be recruited from the same population of paralyzed patients with history of high cervical spinal lesion (C4 and above), and other inclusion and exclusion criteria as outlined in the inclusion criteria (Section 5.0).

13.4 Statistical Power of the Study

With only two subjects, the statistical power of this study to support conclusions for the population of paralyzed patients at large is weak. This study is not intended to bring statistical power to bear on making conclusions about the absolute safety of the device. This is a pilot study intended to evaluate the basic safety and effectiveness of the device. Given the nature of the device and its early state of development, it is appropriate and necessary to initiate a small, longitudinal feasibility study. Therefore, only two subjects will be recruited into the study. The study outcomes for these subjects will be used to evaluate whether more and larger studies are warranted.

13.5 Power to Address Objectives

The primary objective of this study is to evaluate the safety of the NPS. By implanting the device in two subjects and monitoring their health over the course of the study, the primary safety objective will be satisfied.

The secondary objective of this study is to evaluate the effectiveness of the NPS when controlling virtual or physical end effectors. By monitoring the subjects as they perform study tasks using the NPS, the primary effectiveness objectives of this study will be satisfied.

14.0 Registration Guideline

14.1 Patient Registration

The subject will be officially registered upon provision of informed consent to the physician.

14.2 Registration Forms and Records

Registration forms include Consent Information and Inclusion/Exclusion clinical notes (Section 18.4), and the Patient Manual (Section 18.3).

Two copies of the signed and dated patient Informed Consent form with Bill of Rights will be available (an original for patient's medical chart; one copy for the patient; and the other for the PI's file).

15.0 Biohazard Containment

There will be no biohazard materials associated with this clinical study outside of the standard clinical environment. All biohazardous material (e.g., sharps) generated in the clinical environment will be disposed of according to the standard practice and methods set forth by the established clinical protocol.

16.0 Ethical and Regulatory Considerations

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

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18.0 Appendix

The appendices include the following items:

- Clinical Calendar (Section 18.1)
- Informed Consent Document (18.2)
- NPS Patient Manual (Section 18.3)
- Clinical Notes (Section 18.4)
- Rey Auditory Verbal Learning Test Normative Data (Section 18.5)

18.1 Clinical Calendar

Table 18-1 Calendar of Study Procedures and Activities

Procedure	Eligibility	Baseline	Implant	Healing Period	Study Period	Explant	Follow-up
	(N/A)	(N/A)	Week 0	Weeks 0-2	Weeks 3-52	Week 52	Week 53+
Protocol Activities							
Rey Auditory Verbal Learning Test	X						
Symptom Checklist-90-Revised Test	X						
Cognitive Abilities Screening Instrument	X						
Vital Sign Measurements	X	X	X	X	X[2]	X	X[3]
Administer Quality-of-Life Survey		X			X[2]		X
Complete Medical History		X					
Complete Physical Examination		X					
Complete Neurological Examination		X		X	X[2]		X[3]
Electrocardiogram (EKG)		X				X	
Chest X-Ray		X					
Rapid Plasma Reagin (RPR) Test		X					
Complete Blood Count (CBC)		X	X			X	
Complete Metabolic Panel (CMP)		X	X			X	
Urine Pregnancy Test[1]		X	X			X	
Urinalysis (UA)			X			X	
Prothrombin Time (PT)/ Partial Thromboplastin Time (PTT) Test			X			X	
General Anesthesia			X			X	
Brain MRI			X				X
Pre-operative antibiotics (Vancomycin 1 gram IV)			X			X	
Post-operative anti-seizure (Keppra 500 mg PO q12 hours for two weeks)			X			X	
Post-operative antibiotic (NAME? QUANT? 24 hours)			X			X	
Post-operative CT scan				X		X	
Task 1: Fixed Targets					X[4]		
Task 2: Continuous Positioning					X[4]		

1 For women of childbearing age.
2 To occur once per month during the indicated study phase.
3 To occur at 1-week, 6-week, and 3-month intervals after surgery
4 To occur 3-5 times per week for the indicated study phase.

Table 18-2 Calendar of Source Documents

Procedure	**Eligibility**	**Baseline**	**Implant**	**Healing Period**	**Study Period**	**Explant**	**Follow-up**
	(variable)	(variable)	Week 0	Weeks 0-2	Weeks 2-52	Week 52	Weeks 53+
Source Document Schedule							
Adverse Event Clinical Note		*When Applicable*					
Action Research Arm Test (ARAT) Clinical Note					X[1]		
Canadian Occupational Performance Measure (COPM) Clinical Note					X[2]		
Conclusion/Withdrawal Clinical Note						X[3]	
Consent Information Clinical Note	X[4]						
Inclusion/Exclusion Clinical Note	X						
Initial Office Appointment Clinical Note	X						
Office Appointment Clinical Note		X	X	X	X	X	X
Quality-of-life Index (QOLI)		X			X[2]		X
Study Session Clinical Note					X[5]		
Surgical Procedure Clinical Note			X			X	
Hospital Discharge Summary Dictation			X			X	
Implant Procedure Summary Dictation			X				

1 To occur at 10 week intervals beginning the week after healing.
2 To occur once per month during the indicated study phase.
3 Expected to occur when indicated, but may occur at any time during the course of the study due to patient election, adverse event, etc.
4 To occur prior to any tests, procedures, or study activities.
5 To occur 3-5 times per week for the indicated study phase.

18.2 Informed Consent Document

18.3 NPS Patient Manual

18.4 Clinical Notes

The following clinical notes are included in this section:

- Adverse Event
- Action Research Arm Test (ARAT)
- Canadian Occupational Performance Measure (COPM)
- Conclusion/Withdrawal
- Consent Information
- Inclusion/Exclusion
- Initial Office Appointment
- Office Appointment
- Quality of Life Index (QOLI)
- Study Session
- Surgical Procedure

18.5 Rey Auditory Verbal Learning Test Normative Data

Tables 18-3 and 18-4 list the exclusion thresholds by age for females and males (respectively). Subjects who score lower than the age-appropriate threshold in any of the A5, A6, or A7 components of the RAVLT will be excluded from the study.

Table 18-3. RAVLT Exclusion Thresholds by Age: Females

	Age Groups						
	16-19	20-29	30-39	40-49	50-59	60-69	70+
Trial A5	11.8	11.4	11.4	10.9	9.5	10.3	8.9
Trial A6	9.6	9.1	10.2	8.7	7.1	8.2	6.0
Trial A7	8.9	10.0	9.7	8.8	7.5	8.0	6.2

Table 18-4. RAVLT Exclusion Thresholds by Age: Males

	Age Groups						
	16-19	20-29	30-39	40-49	50-59	60-69	70+
Trial A5	11.2	11.0	8.8	8.9	9.2	6.9	5.7
Trial A6	9.6	9.4	7.4	7.2	6.7	4.4	4.7
Trial A7	9.6	9.2	8.1	7.8	7.4	3.3	3.0