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Microelectrode Brain-Machine Interface for Individuals With Tetraplegia

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- IDE G100298 Investigational Plan (protocol)

IDE G100298 / S013

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This is an updated clean version of the IDE. Note that only section E was modified.

INVESTIGATIONAL DEVICE EXEMPTION (IDE) SUPPLEMENT
G100298, S013, January 15, 2014

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E. Investigational Plan

1.0 Purpose of the Investigation

1.1 Name of investigational device

Blackrock Microsystems NeuroPort Microelectrode Array System (Neuroport Array)

1.2 Intended use of the investigational device

In the proposed study, the efficacy of using NeuroPort Arrays (K070272) for chronic (>30 days) recording of neural signals in humans will be investigated. No modifications are being made to the Arrays as part of this investigation.

We will implant 2 NeuroPort Arrays in the motor cortex of individuals with limited or no ability to use both hands due to cervical spinal cord injury or brainstem or spinal stroke. The NeuroPort Arrays will be implanted for 1 year (+/- 30 days). Study participants will learn to control their neural signals (brain electrical activity) recorded from the NeuroPort Arrays in order to control a variety of external devices including virtual reality objects, a motorized prosthetic limb and a robotic arm exoskeleton in a safe environment. Demonstration of successful control of these devices will support our hypothesis that implantation of two NeuroPort Arrays allows for recording of sufficient neural information to control a complex BMI that can augment impaired motor functions.

For the proposed extension study, we are requesting a supplement to this IDE to allow for implantation duration of up to 5 years. This extension study will allow us to quantify BMI performance and signal quality over a longer duration.

The 510(k) approval for the NeuroPort Arrays describes the indications for use as:

> "The intended use of the Cyberkinetics Neurotechnology Systems, Inc. NeuroPort Microelectrode Array System is for temporary (<30 days) recording and monitoring of brain electrical activity". This 510(k) was purchased by Blackrock Microsystems from Cyberkinetics Neurotechnology Systems, Inc.

For the proposed investigation, the investigational indication for use would be:

> "For chronic (>30 days) recording and monitoring of electrical activity from the motor cortex, in individuals with cervical spinal cord injury or stroke, to control external devices such as computers, assistive devices, and potentially robotic devices".

The neural signals will be processed and recorded by the NeuroPort System as indicated by the current 510(k) approval (K090957). The NeuroPort System includes a patient cable which connects to the percutaneous pedestal connector of the NeuroPort Array, a neural signal processor, a front end amplifier/digitizer, and a computer and display monitor. The indications for use of the NeuroPort System are:

> "The Blackrock NeuroPort Biopotential Signal Processing System supports recording, processing, and displaying of biopotential signals from user supplied

electrodes. Biopotential signals include: Electrocorticography (ECoG), electroencephalography (EEG), electromyography (EMG), electrocardiography (ECG), electrooculography (EOG), and evoked potential (EP)."

Because the NeuroPort System will be used as indicated by the 510(k), the IDE focuses solely on the NeuroPort Arrays.

1.3 Objectives of the clinical investigation

The proposed clinical investigation is a feasibility study directed toward:

Specific Aim 1: Investigate the safety and efficacy of using NeuroPort Arrays for chronic recording of neural activity from the motor cortex of individuals with upper limb impairments.

- Specific Aim 1a: Document the safety of using the NeuroPort Arrays for chronic recording of neural activity. Monthly neurological and physical examinations will be conducted and documented for the duration of the trial. Any serious adverse events that occur as part of this investigation will be reported in accordance with the FDA's expedited reporting requirements.

- Specific Aim 1b: Characterize signal quality recorded with the NeuroPort Array during long term implantation in the motor cortex of individuals with tetraplegia. Primary measurements of signal quality include the number of units recorded by the array and the firing rate of single neurons measured during specific tasks (such as imagined hand movement) [6, 45, 46].

Specific Aim 2: Demonstrate that individuals with tetraplegia can learn to successfully control a variety of external devices and computer-driven tasks using signals recorded with two NeuroPort Arrays. We aim to achieve high-dimensional control of complex systems including both a virtual and robotic dexterous hand and arm to perform grasping and reaching tasks which are essential for activities of daily living. This will be measured over the duration of implantation by computing success rate for a given task as well as the amount of computer assist that is required.

Specific Aim 3: Use MEG to localize areas of the brain that can be voluntarily modulated. These results will be compared to pre-surgical mapping results with fMRI and provide additional information for planning the location of electrode implantation.

- Specific Aim 3a: At the optional follow-up MEG visits, we will use the same paradigms to localize areas of the cortex that can be voluntarily modulated to determine if BMI training has induced neuroplasticity. We expect the areas of cortex responsible for voluntary movement will be more strongly activated with more localized responses.

Specific Aim 4: Conduct a sleep study to measure the quantity and quality of sleep each night for a specified period of time to help clarify the role of sleep in motor learning.

This study will include a sleep diary and brain activity measured during sleep using EEG and/or intracortical recordings from the NeuroPort electrode arrays.

The aims remain the same for the proposed extension study, however we will have the opportunity to investigate these aims during the 1-5 year post-implant period. We also expect that we may see a decline in BMI performance over time as signal quality declines. This will be an opportunity to see if neuroplasticity, or novel training methods, can compensate for this degredation in performance.

1.4 Anticipated duration of the clinical investigation

It is expected that the study will last 3 years. If participants choose to enroll in the extension study, their total participation time could be up to 6 years.

2.0 Clinical Protocol

This section describes the core clinical protocol as already approved by the FDA and University of Pittsburgh IRB. Section 3.0 describes the clinical protocol for the proposed extension study.

2.1 Title of clinical protocol

Microelectrode Brain-Machine Interface for Individuals with Tetraplegia

2.1.1 Protocol number

University of Pittsburgh, PRO10080021

2.1.2 Version number and date

Version 10, November 12, 2013 (Exp Date: November 11, 2014)

2.2 Study design

2.2.1 General study design

This study is a prospective, non-randomized, open-label feasibility study that will be conducted at the University of Pittsburgh.

2.2.2 Study design schematic

Figure 2 illustrates the proposed study design. All procedures are discussed in detail in Section E 2.4.

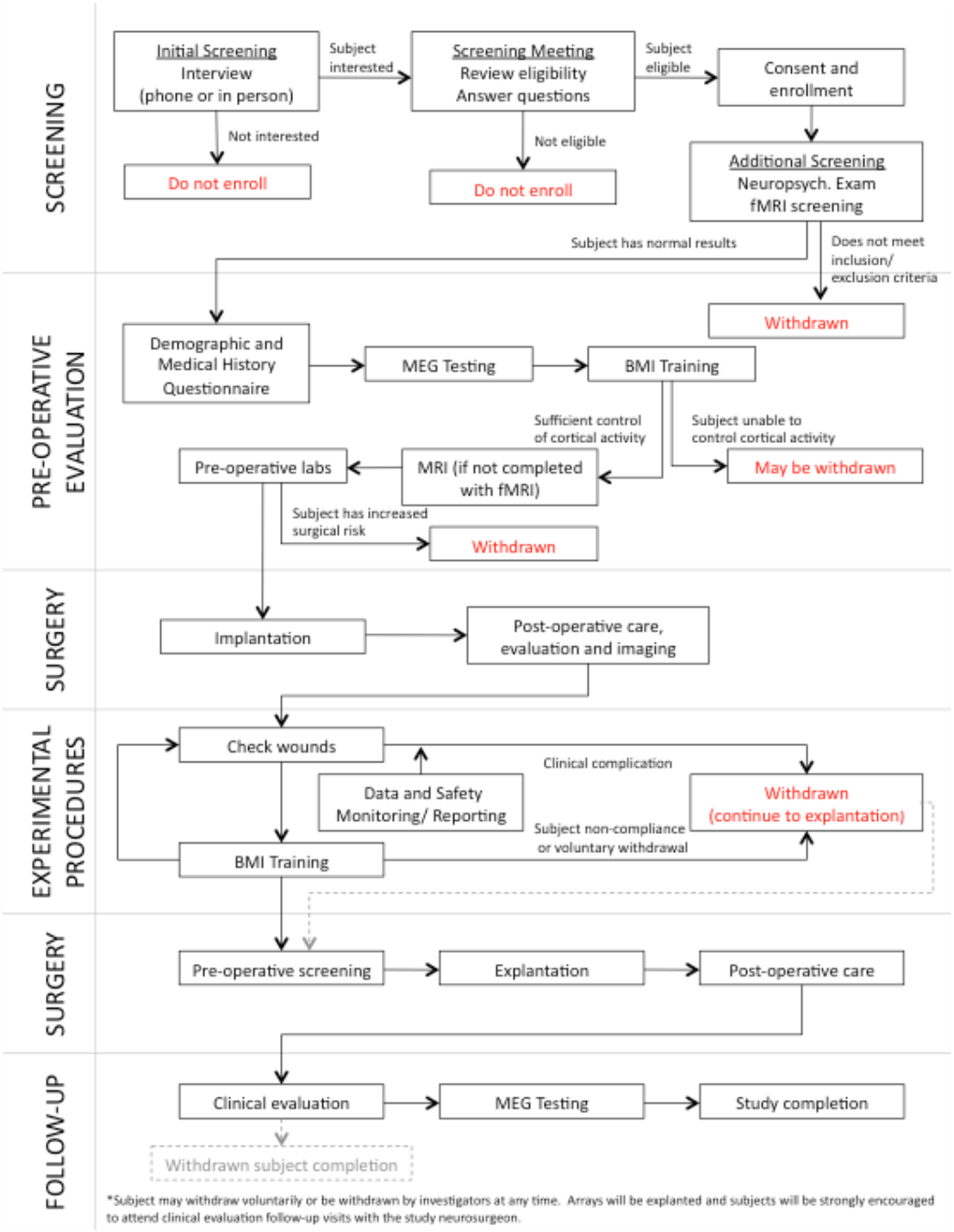

Figure 2: Study Design Schematic

2.3 Subject selection

2.3.1 General characteristics of the proposed subject populations(s)

The subjects for this study will be individuals between the ages of 18-70 with limited or no ability to use both hands due to cervical spinal cord injury or brainstem or spinal stroke. Participants will be screened for a number of co-morbities to ensure their safety during participation. We are using adult subjects because this is a greater than minimal risk study and we want to ensure that the subject is mature enough to understand the tasks, as well as the risks involved in this study. Further, we want to ensure that the neuromotor system is fully developed prior to enrolling in this study. We will not be recruiting military or civilian personnel working for the Department of Defense (DOD).

2.3.2 Anticipated number of research subjects

A maximum of 10 participants will be enrolled in order to implant a maximum of 5 subjects. It is anticipated that we will implant no more than 1 subject every 6 months. Recruitment rates will be monitored by our DSMB. Because it is possible that a subject may enroll and then be determined to be ineligible for anesthesia and/or surgery, the maximum number of subjects enrolled may exceed the number implanted. Subjects will be enrolled as necessary to maintain the target number of subjects implanted. Recruitment will not begin until we have received IRB approval.

2.3.3 Inclusion criteria

1) limited or no ability to use both hands due to cervical spinal cord injury or brainstem or spinal stroke; The subjects must have less than or equal to grade 4 muscle strength in elbow extension and wrist extension and less than grade 2 strength in finger flexor and abduction on the contralateral side to the implant [47]. We will include both complete and incomplete subjects
2) subjects must report that they are unable to perform functional activities with the hand contralateral to implantation.
3) subjects must be over 1 year post-injury at time of implantation. In addition, subject must report no change in neurologic status (strength or sensation) for the previous 6 months.
4) age 18-70 years old. Participants outside this age range may be at an increased surgical risk and increased risk of fatigue during BMI training.
5) live within 1 hour of the University of Pittsburgh and be willing to travel to the University of Pittsburgh once per week for BMI training
6) expect to stay within 1 hour of and be willing to travel to the University of Pittsburgh for at least 18 months after enrollment
7) ability to communicate with the investigators verbally in English because of the need to follow instructions of the study team

8) show an understanding of the study goals and the ability to follow simple directions as judged by the investigators

9) have normal results on neuropsychological and psychosocial assessment (e.g., Wechsler Test of Adult Reading (WTAR) with a score of 90 or above and Brief Symptom Inventory (BSI-18) with a T-score less than 70); the WTAR measures intellectual functioning and the BSI-18 measures mental health; psychosocial health and support will be assessed by interview with the psychologist

10) able to activate distinct cortical areas during imagined or attempted movement tasks (i.e. hand movement and speaking or moving the mouth); this will be evaluated with functional magnetic resonance imaging (fMRI) as part of screening

11) must have a stable psychosocial support and caregivers who are able to perform the necessary daily care of the participant's skin and pedestal site; This requires that the subject identify a caregiver and a back up who have been in place for greater than 6 months and are able to provide needed physical and psychosocial support. This will be assessed by the study PI and neurosurgeon.

12) have a life expectancy greater than 12 months as assessed by the study investigator and neurosurgeon sub-investigator

13) documentation of informed consent is obtained from the participant or their legal representative

2.3.4 Exclusion criteria

1) visual impairment such that extended viewing of a computer monitor would be difficult even with ordinary corrective lenses

2) presence of other serious disease or disorder that could affect ability to participate in this study (verified during pre-op anesthesia evaluation to determine surgical risk status)

3) recent history of pressure sores that could be exacerbated by 1-2 days of bed rest

4) metallic implants that would prohibit the subject from having a fMRI scan; spinal fixators are generally non-ferrous and would not exclude someone from participating in the study

5) individuals who have any type of implantable generator such as a pacemaker, spinal cord stimulator, cochlear implant, deep brain stimulator, vagus nerve stimulator, or defibrillator

6) women of childbearing age who are pregnant, lactating, or plan to become pregnant during the next 25 months

7) allergy to contrast medium or kidney failure that could be exacerbated by contrast agent (for MRI)

8) receiving medications (such as sedatives) chronically that may retard motor

coordination and cognitive ability

9) individuals who require routine MRI, therapeutic ultrasound, or diathermy
10) individuals with osteomyelitis
11) having a severe skin disorder that causes excessive skin sloughing, lesions or breakdown of the scalp
12) history of myocardial infarction or cardiac arrest or with intractable cardiac arrhythmias
13) individuals with an implanted hydrocephalus shunt
14) individuals who have had a stroke cause by a surgical procedure
15) active infection(s) or unexplained fever (verified during pre-op anesthesia evaluation to determine surgical risk status)
16) consuming more than 1 alcoholic beverage per day on average
17) receiving chronic oral or intravenous steroids or immunosuppressive therapy
18) active cancer within the past year (other than adequately treated basal cell or squamous cell skin cancer) or require chemotherapy
19) uncontrolled insulin dependent diabetes mellitus
20) uncontrolled autonomic dysreflexia (for those with spinal cord injury)
21) history of seizures
22) attempted suicide in the past 12 months
23) individuals who are immunosuppressed or who have conditions that typically result in immunocompromise (including, but not limited to: ataxia-telangiectasia, cancer, Chediak-Higashi syndrome, combined immunodeficiency disease, complement deficiencies, DiGeorge syndrome, HIV/AIDS, hypogammaglobulinemia, Job syndrome, leukocyte adhesion defects, malnutrition, panhypogammaglobulinemia, Bruton disease, congenital agammaglobulinemia, selective deficiency of IgA and Wiscott-Aldrich syndrome)
24) individuals with implanted drug delivery pumps

2.4 Study procedures

2.4.1 Screening procedures

We will recruit subjects from two University of Pittsburgh Institutional Review Board (IRB) approved registries developed by the Human Engineering Research

Laboratories (VA IRB #01185) and the Department of Physical Medicine and Rehabilitation (IRB #0304069). All members of the registry have agreed to participate in the registry, and have given permission to be contacted for future research. The recruitment letter for this study will be provided to the registry investigators to distribute to potential subjects according to the procedures established in the registry IRB approved protocols. The recruitment letter will be accompanied by a letter from the registry PI/coordinator stating why they are receiving information about our study. In response to the recruitment letter, potential subjects will directly contact the research team if interested in participating. We may also post the recruitment letter on websites affiliated with our laboratory or the University of Pittsburgh, Department of Physical Medicine and Rehabilitation. Clinicians in the Department of Physical Medicine and Rehabilitation who are knowledgeable about our study may distribute the letter to their patients if they think they may be eligible. Finally, we have another IRB-approved protocol at the University of Pittsburgh (PRO10010043) which is an online survey related to BMI technology. Participants in that study have the option of providing their contact information if they would be interested in participating in future research. We may contact these individuals by phone, or by sending them a recruitment letter. Individuals may contact our study team directly in response to the clinicaltrials.gov website, scientific publications, media, or other means besides our planned recruitment methods.

An initial screening will be conducted to review the study procedures and inclusion/exclusion criteria. The initial screening can be conducted over the phone, or in person, for the individual's convenience. All but three eligibility criteria (muscle strength, fMRI and neuropsychological exam) will be reviewed during the screening and assessed via self-report. A urine pregnancy test will also be given for females during the pre-op labs. If the subject is interested in participating, we will collect his or her contact information and set up a meeting with the study team. We can also mail the consent form ahead of time to potential participants to allow them time to read the form before meeting with the study team. At the meeting with the study team, the potential participant will have a chance to gather more details about the study and ask additional questions. This also allows the study team to meet the potential participant to make sure that they meet the inclusion criteria which include showing an understanding of the study and ability to follow directions. Prior to consenting for the study, the subject will meet with research staff including the neurosurgeon on this project. After the subject has met with the study team, and agreed to participate in the study, they will be consented by the principal investigator. We may visit the participant's home to ensure that there is sufficient space for conducting in-home BMI training.

Careful consideration of the risks/benefits and the informed consent process is required in this study both because of the invasive and investigational nature of the device, the chronic care (home) time commitment involved in utilization of the device, as well as the potential vulnerability of the intended subject population. Because the device will be utilized in the subject's chronic care environment, which may be the subject's home, an understanding of the requirements of participation is

important to the subject as well as a committed family member and/or caregiver. Individuals with tetraplegia require help in their day-to-day activities from someone other than themselves. Because participation in the study requires at least one family member/primary caregiver to take an active role in the study, the informed consent form also requires the signature of a family member or primary caregiver.

It is the responsibility of the principal investigator (PI) that each subject being considered for participation in the study be given a full explanation of the protocol. Informed consent is mandatory after adequate explanation of the objectives, methods, anticipated benefits, and potential risks of the study before any study specific procedures are performed. The informed consent form must include the required eight basic elements. Informed consent will, consistent with site institutional policies and FDA regulations (21CFR, Part 50), be obtained in the following manner.

A meeting will be held with the investigator, potential study participant, his/her family member or primary caregiver, and if required (i.e., if not the family member/primary caregiver), the subject's legal representative that is authorized to sign for the subject. The investigator will discuss the study with all those present. The informed consent form will be reviewed in detail and a discussion of the nature and duration of the study as well as the anticipated risks and benefits will take place. The subject and family member/primary caregiver will be encouraged to ask questions and these questions will be answered. The subject will be encouraged to take additional time, if necessary, to consider participation before signing or having the informed consent signed by their legal representative.

The family member/primary caregiver is agreeing to support the subject in their chronic care environment. This support includes reading and following the instructions for daily wound monitoring and weekly cleaning designed to minimize the risk of infection. The family member/primary caregiver and the subject will also be responsible for informing any other caregivers or nursing staff about the subject's participation in the study and the steps required to minimize the risk of infection.

Once written informed consent is obtained, the subject is enrolled in the study and is assigned a subject ID. A physician-investigator will then verify the eligibility of the subject by assessing all of the eligibility criteria. The subject's muscle strength will be tested by a physician-invesigator or therapist. Two additional screening procedures will be conducted after informed consent, but prior completing the study procedures.

(1) Neuropsychological examination: Participants will complete a neuropsychological assessment with a trained psychologist. We will use the Wechsler Test of Adult Reading (WTAR) and Brief Symptom Inventory (BSI-18) to assess intellectual functioning and psychological distress. If the subject does not have a normal result on the neuropsychological examination, they will be excluded. The WTAR measures intellectual functioning and the BSI-18 measures mental

health. Psychosocial health and support will also be assessed by interview with the psychologist. This examination is expected to take less than 30 minutes and will be performed in University of Pittsburgh or UPMC research space.

(2) Pre-surgical screening to localize cortical activity during imagined or attempted movement: fMRI will be used as the gold standard to localize the cortical area where the NeuroPort Arrays will be implanted. fMRI testing will be completed at the Magnetic Resonance Research Center at UPMC Presbyterian Hospital. Subjects will be asked to complete simple tasks during the fMRI scan. For example, subjects may be asked to view, imagine, or attempt hand and upper limb movements, speaking, or tongue movements. The goal of the fMRI scan is to create a map of motor cortical areas in order to guide the surgical procedure. The fMRI is expected to take less than 1 hour.

2.4.2 Experimental procedures

Pre-surgical procedures and electrode implantation will occur within 6 months after the subject undergoes screening procedures. We will work with each individual to determine the optimal testing schedule. We will photograph or videotape portions of the experimental sessions. Appropriate UPMC permission will be obtained as needed for any photographs or videotaping of participants. All experimental procedures are described below.

Demographic and Medical History Questionnaire:

The subject will be asked to provide basic demographic information (age, weight, height, etc.) via self-report. We will also ask questions about their medical history including the date of injury or diagnosis and their current level of function. Finally, we will ask questions related to improvement of quality of life and BMI technology. A complete copy of the questionnaire is included with the Case Report Forms in Appendix I. This questionnaire is expected to take less than 30 minutes to complete and can be completed at any of the study visits.

Pre-surgical Magnetoencephalography (MEG) Testing:

Subjects will participate in a MEG scan prior to surgery where they will be asked to perform simple imagined or attempted movements which will provide additional data related to the ideal site for electrode implantation. Similarly, they may be asked to observe actions performed by others. These actions will be simple movements such as hand grasp or tongue movement. As part of the standard protocol for MEG testing, we may attach additional sensors (using tape or an adhesive) to record head position, electroencephalography (EEG), electrocardiography (EKG), electromyography (EMG), or electro-oculography (EOG). EEG is an additional measurement of neural activity. The other recordings allow us to correct for noise sources or head movement. MEG and all of the related recordings are completely non-invasive. The MEG test allows us to measure cortical sources of activity with high spatial and temporal resolution. MEG testing

following the same procedure will be performed again after BMI testing is completed to determine if plasticity has been induced. For example, we would expect the sources responsible for imagined movement to be stronger following BMI training. The pre-surgical MEG session is expected to take less than 2 hours. All MEG scans will take place at the UPMC Brain Mapping Center at UPMC Presbyterian Hospital.

For some subjects, MEG testing may be contraindicated. Reasons for contraindication include: having a head circumference greater than 60 cm (in order to fit in the MEG helmet), having metallic implants in the head or neck region, or being ventilator dependent. If the subject is unwilling or unable to participate in MEG testing, they can still be included in the study. While the MEG experiments would provide additional information regarding plasticity, this is not the main priority of this research. We can assess similar measures of plasticity using neural data recorded during BMI training.

Pre-surgical Brain-Machine Interface (BMI) training:

Study participants may complete up to 5 sessions of BMI training using electroencephalography (EEG) and/or MEG prior to implantation of the NeuroPort Arrays. They will learn to modulate activity in the motor cortex to complete simple tasks (such as 1D or 2D cursor control). While these neural recording methods will not allow for high dimensional control, these training sessions will allow participants to learn to voluntarily modulate their neural activity using non-invasive technology. If participants are unable to voluntarily modulate their motor cortical activity during the pre-surgical BMI training, the investigators may decide to withdraw the participant from the study or conduct additional training with EEG/MEG prior to implantation.

Pre-surgical MRI scan:

A 3-D structural MRI of the subject's brain and skull will be taken at a clinical facility at UPMC following a standard protocol for use with the image guidance surgical tool. Since the structural MRI for image guidance and fMRI scan take place at the same facility, we may complete both during the same visit. The scan, including preparation time, is expected to last less than 1 hour. This MRI will be used in conjunction with image guidance technology to localize the surgical site. This type of scan requires the use of an FDA-approved contrast agent. The agent is given through a needle (IV) placed in the arm. The IV is placed using standard hospital techniques.

Pre-operative labs and screening:

Participants will undergo standard pre-surgical screening at the Anesthesia Pre-Op Clinic at UPMC. The clinic staff will perform a medical history interview and a simple physical examination. Participants will be asked to provide a blood and urine sample. Standard lab tests will be run on these samples to ensure that

participants do not have risk factors that would make them an unsuitable candidate for surgery. Women of childbearing age will be required to undergo a urine pregnancy test. Participants will be withdrawn if it is determined that there are unexpected increased surgical risks. Sometimes the clinic requires an EKG to monitor cardiac activity. They may also request a chest x-ray as part of this screening. If the participant has an active urinary tract infection, they will be required to pursue appropriate treatment (antibiotics) at their own cost prior to having surgery. This visit is expected to last 1 hour and will be performed at UPMC Montefiore up to 30 days before the implantation surgery. This screening will guide selection of anesthesia which will be selected by the anesthesiologist to minimize propofol infusions and benzodiazepines. Additional tests and treatments may be ordered by the PI or neurosurgeon to ensure participant safety.

Surgical Procedures:

The NeuroPort Arrays will be implanted by our neurosurgical team at UPMC Presbyterian Hospital. The subject will be fully anesthetized throughout the surgery. Antibiotics (1-2 grams of 1st generation cephalosporin, i.e. cefazolin) will be given intravenously in the operating room within 60 minutes prior to the first incision to minimize the risk of infection. A different appropriate broad spectrum antibiotic may be used if the subject is allergic to cefazolin.

Hair near the implantation site will be shaved to minimize the risk of infection. A small craniotomy (approximately 5 cm x 5 cm) will be performed over the motor cortical areas identified during the screening procedures. Image-guidance techniques that allow the surgeon to view 3-D coordinates of a physical stylus on the imaging studies will be used to allow for precise positioning of the craniotomy and electrode arrays. The structural MRI, fMRI, and MEG scans will be used with the image guidance system as needed. A head holder (Mayfield Head Clamp) will be used to keep the subject's head still during the surgery and allow for use of the image guidance protocol. This clamp is fixed to the subject's skull during surgery and will leave 3-4 small puncture wounds away from the site. These sites heal quickly and generally do not leave scars. The dura will be cut and elevated to allow for positioning of the NeuroPort Arrays. A neurophysiologist may perform intraoperative mapping to further verify that the NeuroPort Array is positioned in the optimal location. This involves using electrodes on the cortical surface to record neural activity while a nerve in the arm (typically the median nerve) is stimulated using surface electrodes. This type of intraoperative mapping will be used only if the participant has an incomplete spinal cord injury or reports some level of residual motor or sensory function in the upper limb. Impedance testing may also be conducted during surgery. Impedance testing measures voltages when very small currents are driven to the electrodes for a short period of time. It is an approved function of the array and no additional risks are expected. The targeted locations for implantation will be on a relatively flat portion of a gyrus away from large blood vessels.

The NeuroPort Array is implanted using a NeuroPort Inserter Assembly. The

pneumatically-actuated inserter wand is designed for consistent and controlled implantation of the NeuroPort Array. When the button on the trigger cable is pushed, the inserter wand applies a consistent pulse and travel distance (1.5 mm) to the NeuroPort Array, inserting it into the parenchyma in less than 1 millisecond. During surgery, the inserter assembly attaches to the Mayfield Head Clamp via the inserter wand holder which serves two key functions. It firmly secures the inserter wand to prevent recoil during the NeuroPort Array insertion process, and it facilitates precision alignment of the inserter wand with respect to the back of the NeuroPort Array just prior to pneumatic impulse insertion.

Each NeuroPort Array connects to its own Patient Pedestal. The positioning of the Patient Pedestals will be chosen based on number of factors. First, they will be positioned along the midline of the skull as this is a flat, thick area of bone and it will not interfere with the subject's comfort when they are lying down. Second, the Patient Pedestals will be as positioned as far away from the craniotomy site as possible, as this has been shown to reduce the risk of infection [48, 49]. The gold lead wires will be tunneled beneath the scalp in order to separate the craniotomy and Patient Pedestal sites. This distance will be maximized while ensuring that there is enough slack in the gold wire bundle for strain relief. Third, the Patient Pedestals will be secured to the skull at least 5 cm apart. This allows for sufficient space to connect the Patient Cable which connects the Patient Pedestal to the NeuroPort System. The space between the Patient Pedestals will be larger than the pedestal diameter to minimize the risk of necrosis. The general rule of thumb is that a flap should be no longer than it is wide and when making parallel incisions the distance between should be equal to the length to prevent devascularization of tissue in between. The Patient Pedestal will be affixed to the skull with titanium screws. Titanium cranial straight plates may be used to fix the gold wire bundle to the skull. Each NeuroPort Array has two silver reference wires that can be placed subdurally or epidurally. Figure 3 shows an example of an implanted array and pedestal, although in our protocol, the pedestal will be positioned further away from the craniotomy site.

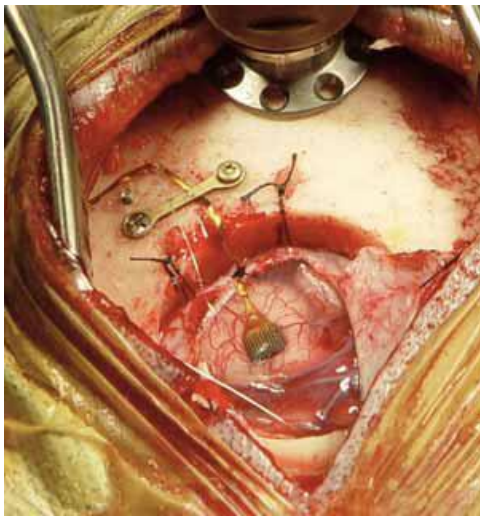

Figure 3. Patient Pedestal and NeuroPort Array Placement

The dura will be reapproximated before the bone flap is repositioned over the implantation site and secured using suture or titanium or absorbable miniplates. The skin around the Patient Pedestal will be reapproximated and closed with skin sutures or staples. The pedestal will be covered with the patient pedestal cap, which will remain in place anytime the Patient Cable is not connected (Figure 4).

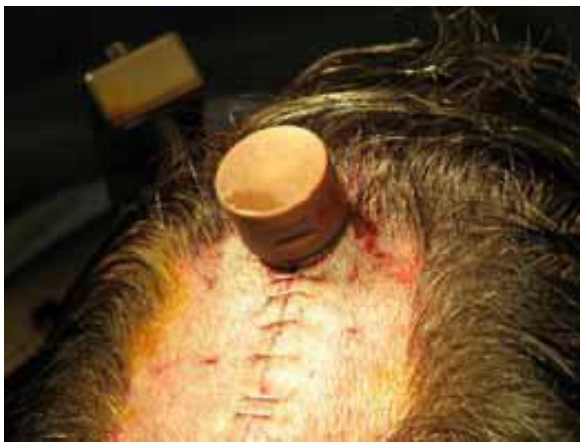

Figure 4. Patient Pedestal and Cap Post-Surgery

The entire surgical procedure is expected to last 4-8 hours.

Post-Operative Hospital Stay:

Post-operative care will depend on the participant's condition, however we expect most subjects to stay in the post anesthesia care unit (PACU) for approximately 3 hours after surgery. They will be transferred to the neurosurgical intensive care unit (ICU) for approximately 24 hours before transitioning to the neurosurgical medical surgery recovery unit where they will stay for 1-2 days. The PACU, ICU, and medical surgery recovery unit are all located at UPMC Presbyterian Hospital. The participants will then stay at the UPMC Rehabilitation Institute for up to 10 days for post-operative rehabilitation. The rehabilitation stay serves primarily as an opportunity for the participant and their caregiver to become familiar with caring for the Patient Pedestal while medical staff can monitor wound healing. We may begin BMI training while the participants are staying at the UPMC Rehabilitation Institute. The study neurosurgeon and PI will determine when the participant will be moved from each post-op unit. The PI and rehabilitation team will determine when the individual can be discharged from the Rehabilitation Institute and sent home.

Post-Operative Imaging:

Study participants will have an x-ray and head CT after surgery to document placement of the NeuroPort Arrays. Lateral and AP head x-ray views will be taken. These imaging procedures will take place in UPMC facilities during the participants' post-operative hospital stay, typically within 48 hours after surgery. Additional CT images will be obtained if there is a change in the subject's neurological examination or the subject experiences severe headaches, nausea, and/or abnormal behavior. These procedures will enable our neurosurgeon and their clinical team to identify infection, bleeding, edema, or neurological

dysfunctions as early as possible and treat them properly.

Post-Implant Clinical Evaluation:

A clinical investigator will perform a monthly clinical evaluation to monitor the participant's neurological and musculoskeletal status. Wound checks will also be performed at this visit. If any changes in neurological status or musculoskeletal functioning are noted, appropriate medical care will be provided. These clinical visits will likely be combined with research visits to the University of Pittsburgh or UPMC.

Psychological Evaluation:

The subject will have opportunities to talk to a psychologist throughout the study, either over the phone or in person. These discussions can be scheduled regularly (approximately 1, 3, 6 and 9 months after implantation as well as prior to explantation) to discuss any concerns the subject may have. The psychologist may refer the subject for additional meetings as necessary. In addition, physician-investigators, including the study PI and neurosurgeon, will be interacting with the subject on a regular basis and can refer the subject to a psychologist at their discretion. If the subject has severe problems or concerns, he or she may be withdrawn from the study.

Brain-Machine Interface (BMI) Training/Testing:

Neural recording from the NeuroPort Arrays may begin as soon as the participant has recovered from surgery. We expect this to take 2-3 days and the first recording session will be scheduled based on the medical opinion of the study neurosurgeon and PI and how the subject is feeling. Neural recording will be conducted for the duration of implantation. The recorded neural data will be used to operate a BMI system that allows the participant to control a computer cursor, virtual object, or assistive device. A summary of selected configurations of this system is provided below. Subject safety is ensured by the physical and electrical isolation offered by the NeuroPort System.

While the NeuroPort Arrays are implanted, we will conduct BMI training for up to 8 hours per day for up to 5 days per week. At least 1 session per week will be conducted while the array is implanted. BMI testing may occur at the University of Pittsburgh, UPMC, or in the participant's home. Rest, meals, and other breaks will be scheduled as needed. We may not conduct training sessions every day. This will be determined by the research staff and the subject.

At the beginning of each BMI testing session, an investigator will connect the Patient Cable to the Patient Pedestal. There are two types of behavioral tasks that the subjects will participate in as part of the BMI Training/Testing:

1. Open-loop tasks:

In the so-called "open-loop" tasks, subjects respond (with movement or other action) to a simple stimulus (such as visual or audio cue). Kinematics and muscle activity may be recorded using a DataGlove (a wearable glove that measures the finger joint movement), EMG electrodes, or motion tracking system. These tasks are used to identify associations between the user's action and neural activity in the brain. The type of data that will be recorded will be dependent on the participant's injury level and completeness. Some participants may not have any residual motor or sensory function in the upper limb and may not perform these tasks. In some cases the kinematic or EMG data will be used to verify that no overt movement is occurring.

Examples of sensory inputs include:

- Visual cue (e.g. prompt on a computer screen)
- Audio cue (e.g. tone or spoken word)
- Somatosensory
    - Passive movement of a limb
    - Peripheral nerve stimulation: Here a small metal disc electrode is placed on the arm or leg to deliver an electrical stimulus which results in an evoked-potential in the brain. The stimulus level will be adjusted so that the subject is able to feel the stimulation, but is not uncomfortable.
    - Vibrotactile feedback

Examples of user responses include:

- Real, imagined, or observed movement (e.g. opening and closing the hand, tapping fingers, or protruding the tongue)
- Cognitive response (e.g. describing an object or saying a word)
- Interaction with a human interface device (e.g. mouse, joystick, or DataGlove)

2. Closed-loop tasks

In the so-called "closed-loop" tasks, the computer cursor (or other output signal) is controlled by neural signals recorded and processed by the BMI system. The subject is trained to willfully modulate their neural signals to achieve the desired output. We have the capability to provide "computer-assist" which blends the neural signals with an optimal control signal in order to ensure some level of successful completion. This will facilitate learning and keep the participant motivated. The assist level will be documented and the goal is to reduce the assist level to 0% so that the participant has full neural control over the output signal.

There are three main categories of tasks that a subject may complete:

- Basic paradigms (e.g. controlling a computer cursor or virtual hand)

- Interaction with computer and computer games (e.g. typing, icon selection, or playing a video game) or a virtual reality environment
- Controlling external devices (e.g. prosthetic limb, robotic arm or exoskeleton)

Neural and behavioral data will be recorded during each BMI session in order to address the Specific Aims. At the beginning of each session (or at least weekly) spike-sorting will be used to identify single-units that are recorded from each electrode. We will track the number of units recorded over the duration of implantation. Further, by comparing the amplitude and shape of the recorded action potential, it is possible to identify whether the single-unit recorded by a given electrode is different from that recorded on a previous day. Spike data (recorded action potentials) along with the calculated firing rate for each neuron will be recorded during the behavioral tasks and compared over the duration of the implant. Behavioral and neural data that is recorded during closed-loop control will be used to address Specific Aim 2. Behavioral data may include kinematics of a cursor, virtual object, robotic arm, etc. We will also compute the success rate achieved by the participant for a given task over a number of sessions. In addition, part of the training paradigm involves initial control being achieved with computer assistance. We expect that the amount of computer assistance will decrease over time as success rates with a task improve or stay constant. The amount of computer assistance needed is an easily measured variable that we will track as an indicator of success. Impedance measurements will be collected during BMI testing sessions throughout the study. Impedance testing is an approved function of the NeuroPort recording system and can be used to assess array function and encapsulation.

We will also document volunteered or observed adverse events at least weekly as part of the BMI training sessions as a measure of device safety. Monthly neurological and physical examinations will be conducted for the duration of implantation and will likely be conducted at the same visit as a BMI training session.

At the end of each session, an investigator will remove the Patient Cable and clean the device. At a minimum, the Patient Pedestal should be cleaned every 7 days by a family member, caregiver, medical professional, or study team member. We will provide detailed cleaning instructions to the participant and anyone who may assist with the cleaning. Sterile procedures will be followed and an antiseptic solution, such as ChloraPrep, will be used to wipe the outside of the Patient Pedestal, the surrounding skin, and the first 8-10 inches of the Patient Cable. An antimicrobial dressing, like the BioPatch, will be placed around the Patient Pedestal. The Pedestal Cap will remain in place whenever the Patient Cable is not connected. The Patient Cable can be cleaned using alcohol or an antiseptic solution.

We will monitor the subject's temperature once per day (on days that BMI testing occurs) as this can be an early indicator of infection. We will instruct the subject to monitor and record their own temperature daily as well. A family member or caregiver will be asked to inspect the Patient Pedestal sites on a daily basis to

identify any changes that may indicate an infection such as erythema, drainage, ecchymosis, pain, or unusual redness along the lead tunnel or pedestal. The study neurosurgeon and PI will train the research team and family member or caregiver in how to monitor wound healing.

Explantation of the electrodes:

Subjects will undergo a second surgery at UPMC Presbyterian Hospital approximately 1 year after implantation of the NeuroPort Arrays. It is possible that the NeuroPort Arrays may be explanted earlier due to technical problems, clinical complications, investigator-initiated withdrawal, or subject-initiated withdrawal. The participant will go through standard pre-operative screening procedures which may include a blood draw. The subject will be fully anesthetized throughout the surgery and will receive antibiotics intravenously as with the implantation surgery. The hair will be clipped in the area of the planned surgery. A skin incision will be made from the Patient Pedestal to the area of the craniotomy. It is possible that fibrous tissue will have formed around the wire bundles and NeuroPort Arrays and this will be dissected away prior to explantation. Impedance testing may also be conducted during surgery. Impedance testing measures voltages when very small currents are driven to the electrodes for a short period of time. It is an approved function of the array and no additional risks are expected. The bone flap will be dissected from the dura and lifted and the dura will be opened. The NeuroPort Arrays will most likely be encased in a membrane that appears to be continuous with the arachnoid. The membrane will be cut open and the NeuroPort Arrays will be removed with forceps. The bone flap will be repositioned and secured with titanium or absorbable miniplates. The skin will be repositioned and closed with skin sutures or staples. The entire surgical procedure is expected to take approximately 3 hours.

Post-operative care will depend on the participant's condition, however we expect most subjects to stay in the post anesthesia care unit (PACU) for approximately 3 hours after surgery. They will be transferred to the neurosurgical intensive care unit (ICU) for approximately 24 hours before transitioning to the neurosurgical medical surgery recovery unit where they will stay for 1-2 days. The PACU, ICU, and medical surgery recovery unit are all located at UPMC Presbyterian Hospital. The participants will then stay at the UPMC Rehabilitation Institute for up to 3 days for post-operative rehabilitation. The rehabilitation stay serves primarily to ensure that the participant is ready to resume normal daily activities while medical staff can monitor wound healing. The study neurosurgeon and PI will determine when the participant will be discharged and sent home.

2.4.3 Follow-up procedures

Post-surgical MEG testing:

We will ask the subject to come back for up to 3 MEG sessions within 6 months after completion of the BMI training. The follow-up MEG sessions are optional

visits for the subjects. If the subject is interested in participating, we will plan to schedule the visits at 2 weeks, 6 weeks, and 3 months after the explantation surgery. The same tasks that were completed during the pre-surgical MEG session will be repeated. In addition to measuring changes in single unit activity over the duration of the study, the MEG studies will allow us to determine if plasticity was induced due to BMI training in terms of volitional modulation of motor cortex activity. These visits are expected to last up to 2 hours each.

Clinical follow-up:

Follow-up visits will be scheduled in order to ensure that the bone flap and Patient Pedestal sites are healing properly. These visits will be scheduled at the discretion of the study neurosurgeon and the subject. We expect that each subject will have two follow-up visits with the study neurosurgeon and their clinical team at 1 and 4 weeks (+/- 3 days) after explantation. Depending on the healing process of the implantation site and percutaneous port, additional imaging studies (x-ray, CT scan, or MRI) may be performed although this is unlikely.

Post-explant counseling:

Subjects will be scheduled for an appointment with a licensed rehabilitation psychologist to assure that they have an opportunity to discuss any concerns they may have post explantation.

2.4.4 Study compliance and withdrawal:

The subject will be under medical supervision for the duration of this study. Their health will be the top priority and participation will be discontinued if surgical intervention is required. The study neurosurgeon and PI will be primarily responsible for evaluating the subject's condition. Complications that could result in removal from the study (and having the NeuroPort Array removed) include:

- Treatment resistant (serious) infection at the implantation site or Patient pedestal
- Array technical malfunction resulting in an inability to collect data that is useful for brain-control tasks
- Serious medical complications that compromise the subject's safety or health

If the participant is non-compliant (e.g., unwilling to participate in BMI training sessions) they may be withdrawn from the study. The NeuroPort Arrays will be explanted and they will be strongly encouraged to attend the follow-up monitoring visit with the study neurosurgeon.

Prior to implantation of the NeuroPort Array, the principal investigator may withdraw the participant if they do not demonstrate an understanding of the study or a willingness to participate. Participants can withdraw from the study at any time. The NeuroPort Arrays will be explanted and they will be strongly encouraged to attend the follow-up monitoring visits with the study neurosurgeon.

We will also ask for guidance from the DSMB if the research team and participant disagree on the decision to explant the NeuroPort Arrays (i.e., if the research team wishes to explant the arrays, but the participant does not).

2.4.5 Schedule of activities (Study Table)

Table 1 summarizes the study schedule.

Table 1: Study Schedule

Study Activities	Screening	Baseline/ Pre-operative Evaluation	Implant	Pre-Discharge	Discharge	Week 1	Week 2	Week 3	Week 4	Month 2-12	Explant/ End of Study
Screening Interview	X										
Informed Consent, Eligibility Assessments	X										
Neuropsychological and Psychosocial Examination (WTAR & BSI-18)	X										
Pre-surgical fMRI Screening	X										
Demographic and Medical History Questionnaire		X									
Pre-surgical Magnetoencephalography (MEG) Testing		X									
Pre-surgical BMI Training		X									
Pre-surgical Structural MRI		X									
Pre-operative Labs and Screening		X									
Implantation of Two NeuroPort Arrays			X								
Post Anesthesia Care Unit (PACU) Stay				X							
Neurosurgical Intensive Care Unit (ICU) Stay				X							
Rehabilitation Stay at UPMC Institute for Rehabilitation and Research				X							
Head X-ray and CT				X							
Ongoing psychological evaluations									X	X	
Neurological and Musculoskeletal Exam; Wound Check by Clinical Investigator					X				X	X	
BMI Training/Testing; Wound Check/Temperature Monitoring by Study Team*						X	X	X	X	X	
Pedestal Cleaning (at least weekly)						X	X	X	X	X	
Daily Temperature Monitoring/Wound Check by Primary Caregiver						X	X	X	X	X	
Explantation of NeuroPort Arrays											X
Post Anesthesia Care Unit (PACU) Stay											X
Neurosurgical Intensive Care Unit (ICU) Stay											X
Rehabilitation Stay at UPMC Institute for Rehabilitation and Research											X

Follow-up Clinical Visits with Neurosurgeon (1 & 4 weeks post-explant) and rehabilitation psychologist											X
Follow-up MEG Testing (2 weeks, 6 weeks, and 3 months post-explant)											X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X

* BMI training may begin immediately after discharge or later as determined by the participant and study team; A wound check will be performed by a study team member weekly after discharge even if BMI training has not begun; BMI training will be conducted at least once per week for the duration of implantation either at the University of Pittsburgh, the University of Pittsburgh Medical Center (UPMC), or in the participant's home; Neural and behavioral data will be recorded during the BMI training/testing sessions in order to address the study specific aims.

2.5 Study outcome evaluations

2.5.1 Study endpoints

The NeuroPort Arrays will be removed 1 year (+/- 30 days) after implantation. A participant will be considered a success for safety if the device is not explanted for safety reasons during the 12-month post-implant evaluation. If the subject experiences treatment resistant (serious) adverse events, he or she will be withdrawn and the arrays will be explanted early (See Section E 2.4.4). The study may also end early if the subject is non-compliant (See Section E 2.4.4).

We believe it is possible that a participant will not want the array removed. If the participant wants the NeuroPort Arrays to stay in, the study PI and neurosurgeon will assess whether this is acceptable. This decision will be based on whether or not the participant is at increased risk by leaving the arrays in and whether the device is still measuring neural activity that is sufficient for brain control. We will consult our DSMB if conflicts arise. One participant in the BrainGate trial has had a NeuroPort Array implanted for more than 1000 days without adverse event [9]. If the NeuroPort Arrays remain implanted for more than 1 year, we will continue to perform clinical follow-up as described in the current protocol. We may also continue brain-machine interface testing although the frequency of the training sessions may be reduced. We will remove the NeuroPort Arrays at anytime as directed by the participant, or as dictated by their clinical condition.

If the participant wishes to leave the NeuroPort Array implanted, but the study PI and neurosurgeon do not feel that it is in their best interest, the participant will be counseled that they should have the NeuroPort Array removed and that not doing so could result in clinically significant adverse events. They will also be informed that brain-machine interface training will not continue. The consent form includes a statement that participants will be financially liable for any medical care resulting from complications of not having the device removed upon instruction of the study PI. We will however allow participants to have the device removed at anytime and the explantation costs would be covered by this study.

2.5.2 Sample size determination

A maximum of 10 participants will be enrolled in order to implant a maximum of 5

subjects. Because it is possible that a subject may enroll and then be determined to be ineligible for anesthesia and/or surgery, the maximum number of subjects enrolled may exceed the number implanted.

New information will be learned with each participant, as this is a feasibility study. Single-subject design statistical analyses will be used. Our main goal is to demonstrate the safety and efficacy of NeuroPort Arrays for long-term recording of neural activity in order to control a high-dimensional BMI.

2.5.3 Outcome data and data analysis

Specific Aim 1a will be fulfilled through monthly clinical examinations as well as observations made by the research staff, participant, or their caregiver throughout the trial. Research staff will document volunteered and observed adverse events at least weekly during the BMI training sessions. Adverse events will be documented and reported to University of Pittsburgh IRB and to the FDA in accordance with the respective reporting requirements and in the annual report. This documentation will serve as documentation of the safety of device in this small sample.

Specific Aim 1b is to characterize signal quality (firing rate, number of units recorded) over the duration of implantation. Data to support this aim will be collected at least weekly during the BMI training sessions. Our primary method of analysis will be to plot the trends in signal quality measures over time. The trend will be quantified using regression techniques.

Specific Aim 2 is to demonstrate that individuals with tetraplegia can learn to successfully control of a variety of external devices and computer-driven tasks using signals recorded with the NeuroPort Array. In additional to video documentation of brain-controlled device operation, we will quantify the number of degrees of freedom achieved by each participant at regular intervals for the duration of implantation. Multiple baselines will be defined as the level of computer assist will decrease with training. We will use regression to quantify changes in performance at a given assist level. Similarly, trends in success rate and computer assist level for a given task will be quantified over the duration of the trial using regression.

Specific Aim 3: Source localization (combining the MEG and structural MRI data) will be used to identify the anatomical foci of cortical activation controlling imagined and/or attempted movement. The coordinates (x,y,z) of the center of activation can be computed with fMRI or MEG relative to the head coordinate system defined using bony landmarks. The location and area of cortical activation measured by fMRI and MEG during imagined and/or attempted movement will be compared for each subject. A paired t-test will be used to compare location and area of cortical activation measured by the two imaging techniques using data from all participants, although the power of this test may be limited by sample size. Qualitative comparisons will be informative and we expect agreement between the two imaging techniques in terms of localizing the area for array implantation. MEG

potentially offers additional information due to higher temporal resolution.

Specific Aim 3a: Cortical modulation will be calculated as the power of the 4-40 Hz frequency band of MEG data that is recorded during imagined and/or attempted movement. Specific Aim 3a will be evaluated by applying repeated measures ANOVA to test for differences in modulation (magnitude and total area) during imagined and/or attempted movement during the pre-surgical procedures and the follow-up sessions.

The study will be considered a success if the device is not explanted for safety reasons during the 12-month post-implant evaluation. Further participants should demonstrate successful control of a high degree of freedom assistive technology in order to safely perform a task that replicates normal activities of daily living, such as grasping a cup with a robotic manipulator. This study is not being proposed to support marketing applications (510(k) or PMA) for the NeuroPort Arrays. Instead, the goal is to demonstrate that three-dimensional microelectrode arrays provide a safe way to record sufficient neural information for controlling complex assistive devices that will increase the independence of individuals with disabilities.

2.5.4 Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Board (DSMB) will be created to review this study. At periodic intervals (to be determined by the subcommittee) during the course of the study, the DSMB responsibilities are to:

1. Review the research protocol, informed consent documents and plans for data and safety monitoring;

2. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome;

3. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;

4. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the PI;

5. Protect the safety of the study participants;

6. Report on the safety and progress of the study;

7. Make recommendations to the PI, IRB, and if required, to the FDA concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;

8. Monitor the confidentiality of the study data and the results of monitoring;

9. Assist the PI by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB will include experts in neurosurgery or neurology, physical medicine and rehabilitation, occupational therapy, bioengineering, and biostatistics. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required.

The University of Pittsburgh, Office of Clinical Research - Health Sciences will provide the logistical management and support of the DSMB. The Chairperson will be the contact person for serious adverse event reporting. Procedures for this will be discussed at the first meeting.

The first meeting will take place after all regulatory approvals are received to establish guidelines to monitor the study. The follow-up meeting frequency of the DSMB will be determined during the first meeting, but it is anticipated that the meetings will occur at a minimum of every 6 months. An emergency meeting of the DSMB will be called at any time by the Chairperson should questions of subject safety arise.

Both the DSMB chairperson and the medical monitor will be physicians capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. The medical monitor shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate. The medical monitor and DSMB may be assigned to assess one or more of the following phases of a research project: subject recruitment, subject enrollment, data collection, or data storage and analysis. The medical monitor may be assigned to discuss research progress with the principal investigator, interview subjects, consult on individual cases, or evaluate adverse event reports. Medical monitors shall promptly report discrepancies or problems to the IRB. They will make recommendations to the IRB and PI about whether to stop a research study in progress, remove individual subjects from a study, or take steps to protect the safety and well-being of research subjects.

Peter C. Gerszten, M.D., who is independent of the study team and has no conflicts of interest, will serve as the DSMB chairperson. His contact information is as follows:

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The position of Medical Monitor will be held by:

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Additional Data and Safety Monitoring by the Study Team:

The core members of this research team will meet at least monthly to discuss study recruitment, study goals and progress, adverse events, participant complaints, modifications, and confidentiality of ongoing studies. The investigators and study team will ensure that proper procedures are in place to ensure data integrity and participant safety. Data will be reviewed and any possible study design changes resulting from our experience or external studies/publications will be discussed. Our priority is to maintain participant safety and confidentiality while collecting data that accurately demonstrates the efficacy of using the NeuroPort Arrays as a direct brain interface. We will comply with the IRB's policy for the reporting of serious and unexpected adverse events as described in Chapter 3.0 of the University of Pittsburgh's IRB Reference Manual. Similarly, we will report adverse device events to the FDA in accordance with the agency's expedited reporting requirements. The outcomes of these meetings will be summarized and included in the annual IRB continuing review. Minutes for these meetings will be kept on file.

3.0 Clinical Protocol For Extension Study

3.1 Title of clinical protocol

Long-Term Microelectrode Brain-Machine Interface (Extension Study)

3.1.1 Protocol number

University of Pittsburgh, PRO12090216

3.1.2 Version number and date

Version 6, January 14, 2013 (Expiration Date: 10/7/2014)

3.2 Study design

3.2.1 General study design

This study is an extension to a prospective, non-randomized, open-label feasibility study that will be conducted at the University of Pittsburgh.

3.2.2 Study design schematic

Figure 2 illustrates the proposed study design for the core study. For the extension study, the Experimental Procedures section (BMI testing, wound checks, clinical exams, etc.) would be expanded from 1 year in duration to up to 5 years. The explant surgery and follow-up visits would continue as described in Figure 2 after the extended implanation period.

3.3 Subject selection

3.3.1 General characteristics of the proposed subject populations(s)

Participants who participated in the core study (IDE G100298, University of Pittsburgh PRO10080021) may be eligible for the extension study if they have had positive clinical and research outcomes after 6 months of implantation and meet the elgibility criteria described in Sections 3.3.3 and 3.3.4.

3.3.2 Anticipated number of research subjects

Up to 5.

3.3.3 Inclusion criteria

1) Participant in PRO10080021 study (IDE G100298) who is at least 6 months post-implant
2) Have no unresolved significant adverse events during participation in PRO10080021
3) Have demonstrated at least 4-dimensional control of a virtual or real robotic arm during participation in PRO10080021
4) Have a stable psychosocial support and caregivers who are able to perform the necessary daily care of the participant's skin and pedestal site; This requires that the subject identify a caregiver and a back up who have been in place for greater than 6 months and are able to provide needed physical and psychosocial support. This will be assessed by the study PI and neurosurgeon.
5) Age 18-70 years old at the time of consent and planned explant
6) Have a life expectancy greater than 12 months as assessed by the study principal investigator and neurosurgeon sub-investigator
7) Live within 1 hour of the University of Pittsburgh, or be willing to travel there, once per week for BMI testing
8) Interested in having the NeuroPort arrays remain in place for 6 months to 4 years beyond the 1 year implantation that is part of PRO10080021. Participants can

decide to extend the implantation for any duration between 6 months and 4 years. This can be decided at any point during the study.

9) Participation is not expected to have an adverse effect on mental well-being as judged by the rehabilitation psychologist
10) Documentation of informed consent is obtained from the participant or their legal representative

3.3.4 Exclusion criteria

1) Women of childbearing age who are pregnant, lactating, or plan to become pregnant during the next 60 months
2) Development of any medical condition that would put the participant at increased clinical risk during extended implantation

3.4 Study procedures

3.4.1 Screening procedures

Participants must already been enrolled in PRO10080021 to be eligible. They will meet with one of the physicians on the study (PI or neurosurgeon) to discuss the study procedures and risks of the proposed study. Informed consent will be obtained by the study PI after these discussions to ensure that the participant has time to review the consent form. As in the core study, a family member or caregiver will also sign the consent form acknowledging that they will support the participant as described in the protocol. It is the responsibility of the principal investigator (PI) that each subject being considered for participation in the study be given a full explanation of the protocol. Informed consent is mandatory after adequate explanation of the objectives, methods, anticipated benefits, and potential risks of the study before any study specific procedures are performed. The informed consent form must include the required eight basic elements. Informed consent will, consistent with site institutional policies and FDA regulations (21CFR, Part 50), be obtained in the following manner.

Participants will already have the NeuroPort Arrays implanted for at least 6 months before being approached about the extension study so they will be very familiar with the study procedures and risks. The study PI will inform the participant and their family or caregiver about the study procedures and risks for the extension study. During a separate meeting, after the subject has had time to review the consent, an investigator will meet with them to review any additional questions. Because the device will be utilized in the subject's chronic care environment, which may be the subject's home, an understanding of the requirements of participation is important to the subject as well as a committed family member and/or caregiver. If the subject is interested in participating, the consent will be completed by the subject, a family member or primary caregiver, and the study PI. After completion of the consent, participation in the study is initiated. As part of screening, the subject will complete a evaluation by the rehabilitation psychologist to document that participation in an extended duration study is not expected to have any adverse

effect on the participant's well being and that they understand the limited duration of the extension study (up to 5 years post-implant) and the risk that their performance in BMI related activity may degrade over time. All of these interactions between the subject and study personnel will serve to further educate the subject. The subject may withdraw at any time.

After consent, eligibility criteria will be verified by self-report, using data from PRO10080021, checking the participant's medical records as necessary, or via interview as described below.

(1) Psychology interview: The rehabilitation psychologist will provide independent determination of eligibility on the basis that the participant understands the study procedures and limited duration. The psychologist will give a recommendation of "eligible" if they believe that participation in the extension study will have no adverse effect on the participant's mental well-being.

3.4.2 Experimental procedures

This study is an optional extension to PRO10080021. Consent and screening for this study may occur as early as 6 months after implant and up to 13 months after implant (the maximum duration allowed in the original protocol). BMI testing will occur as described in the original protocol with similar ongoing clinical monitoring and follow-up as described below:

Brain-Machine Interface (BMI) Training/Testing:

Neural recording will be conducted for the duration of implantation. The recorded neural data will be used to operate a BMI system that allows the participant to control a computer cursor, virtual object, or assistive device. While the NeuroPort Arrays are implanted, we will conduct BMI training for up to 8 hours per day for up to 5 days per week. At least 1 session per week will be attempted while the array is implanted. BMI testing may occur at the University of Pittsburgh, UPMC, or in the participant’s home. Rest, meals, and other breaks will be scheduled as needed. We may not conduct training sessions every day. This will be determined by the research staff and the subject. Also, we may not conduct testing sessions for up to 8 weeks per year. Since participants will have already completed 1 year of testing, we hope to minimize the burden on participants while still collecting valuable data related to signal quality and BMI control. The subject will go no longer than 3 weeks between testing sessions. This will assure that the study team can continue to monitor the wound site and well being of the participant.

At the beginning of each BMI testing session, an investigator will connect the Patient Cable to the Patient Pedestal. We may also record neural activity using EEG electrodes which are placed on the scalp in order to measure larger networks of brain activation. There are two types of behavioral tasks that the subject will participate in as part of the BMI training/testing: 1. Open-loop and 2. Closed Loop. These tasks are the same as described in Section 2.4.2.

Neural and behavioral data will be recorded during each BMI session in order to address the Specific Aims. As described in Section 2.4.2, we will track neural data, including the number of single units and the average firing rate over the duration of the implant. Behavioral data may include kinematics of a cursor, virtual object, robotic arm, etc. We will also compute the success rate achieved by the participant for a given task over a number of sessions. Impedance measurements will be collected during BMI testing sessions throughout the study. We will also document volunteered or observed adverse events at least weekly as part of the BMI training sessions as a measure of device safety. Subject may be asked at test sessions about level of fatigue, quality of sleep at home or other factors that may affect quality of testing performance.

At the end of each session, an investigator will remove the Patient Cable and clean the device. At a minimum, the Patient Pedestal should be cleaned every 7 days by a family member, caregiver, medical professional, or study team member. We will provide detailed cleaning instructions to the participant and anyone who may assist with the cleaning. We will monitor the subject's temperature on days that BMI testing occurs as this can be an early indicator of infection. In addition, we will instruct the subject to monitor and record their own temperature daily as well. A family member or caregiver will be asked to inspect the Patient Pedestal sites on a daily basis to identify any changes that may indicate an infection such as erythema, drainage, ecchymosis, pain, or unusual redness along the lead tunnel or pedestal. The study neurosurgeon and PI will train the research team and family member or caregiver in how to monitor wound healing.

Sleep Diary:

We may ask the participant to maintain a sleep diary which measures the amount and quality of sleep each night.

In-Home Sleep Evaluation:

An in-home sleep evaluation may be performed to evaluate how sleep, or lack of sleep, impacts a participant's performance with the neuroprosthetic device. We may measure the participant's brain activity during sleep (in their home) using EEG and/or intracortical recordings from the NeuroPort electrodes. This testing may be completed by a study team member in the subject's home, or in the case of EEG monitoring, it could be conducted by the subject and a caregiver once the electrodes are setup by a study team member. In addition to brain activity, we may record additional physiological information including electrocardiogram (EKG) activity, temperature (using a small sensor near the nose), and respiration (using elastic belts around the chest and abdomen). We will plan to set up the equipment early enough so as not to interfere with their normal sleep routine. The equipment will be removed after their normal wake-up time. We may ask the subject to perform simple BMI tasks before and after periods of normal sleep. Our goal is to determine how normal sleep (including normally occurring variations in sleep quantity and quality) affects neural activity and BMI performance.

Ongoing Clinical Evaluations:

A clinical investigator will perform a monthly clinical evaluation to monitor the participant's neurological and musculoskeletal status. Wound checks will also be performed at this visit. If any changes in neurological status or musculoskeletal functioning are noted, appropriate medical care will be provided. These clinical visits will likely be combined with research visits to the University of Pittsburgh or UPMC.

Ongoing Psychological Evaluations:

The subject will have opportunities to talk to a psychologist throughout the study, either over the phone or in person. These discussions will be scheduled regularly (approximately every 3 months) to discuss any concerns the subject may have. The psychologist may refer the subject for additional meetings as necessary. In addition, physician-investigators, including the study PI and neurosurgeon, will be interacting with the subject on a regular basis and can refer the subject to a psychologist at their discretion. If the subject has severe problems or concerns, he or she may be withdrawn from the study.

Imaging:

The study neurosurgeon may order a head x-ray or CT if there is a change in the patient's neurological examination or the patient experiences severe headaches, nausea, and/or abnormal behavior. These procedures will enable our neurosurgeon and their clinical team to identify infection, bleeding, edema, or neurological dysfunctions as early as possible and treat them properly. These imaging procedures will take place in UPMC facilities.

Removal of the electrodes:

Subjects will undergo a second surgery at UPMC Presbyterian Hospital approximately 5 years after implantation of the NeuroPort Arrays. It is possible that the NeuroPort Arrays may be explanted earlier due to technical problems, clinical complications, investigator-initiated withdrawal, or subject-initiated withdrawal. The participant will go through standard preoperative screening procedures which may include a blood draw. Explantation procedures are the same as described in Section 2.4.2.

Post-operative care:

Post-operative care will depend on the participant's condition. The participant will remain in the post anesthesia care unit (PACU) for approximately 3 hours after surgery. They will be transferred to the neurosurgical intensive care unit (ICU) for approximately 24 hours before transitioning to the neurosurgical medical surgery recovery unit where they will stay for 1-2 days. The PACU, ICU, and medical surgery recovery unit are all located at UPMC Presbyterian Hospital. Post-operative imaging may be requested by the study neurosurgeon depending on the

participant's condition. The participants will then stay at the UPMC Rehabilitation Institute for up to 3 days for post-operative rehabilitation. The rehabilitation stay serves primarily to ensure that the participant is ready to resume normal daily activities while medical staff can monitor wound healing. The study neurosurgeon, PI and rehabilitation team will determine when the participant will be discharged and sent home.

3.4.3 Follow-up procedures

Post-surgical MEG testing:

We will ask the subject to come back for up to 3 MEG sessions within 6 months after completion of the BMI training. The follow-up MEG sessions are optional visits for the subjects. If the subject is interested in participating, we will plan to schedule the visits at 2 weeks, 6 weeks, and 3 months after the explantation surgery. The same tasks that were completed during the pre-surgical MEG session will be repeated. In addition to measuring changes in single unit activity over the duration of the study, the MEG studies will allow us to determine if plasticity was induced due to BMI training in terms of volitional modulation of motor cortex activity. These visits are expected to last up to 2 hours each.

Clinical follow-up:

Follow-up visits will be scheduled in order to ensure that the bone flap and Patient Pedestal sites are healing properly. These visits will be scheduled at the discretion of the study neurosurgeon and the subject. We expect that each subject will have two follow-up visits with the study neurosurgeon and their clinical team at 1 and 4 weeks (+/- 3 days) after explantation. Depending on the healing process of the implantation site and percutaneous port, additional imaging studies (x-ray, CT scan, or MRI) may be performed although this is unlikely.

Post-explant counseling:

Subjects will be scheduled for an appointment with a licensed rehabilitation psychologist to assure that they have an opportunity to discuss any concerns they may have post explantation.

3.4.4 Study compliance and withdrawal:

The subject will be under medical supervision for the duration of this study. Their health will be the top priority and participation will be discontinued if surgical intervention is required. The study neurosurgeon and PI will be primarily responsible for evaluating the subject's condition. Complications that could result in removal from the study (and having the NeuroPort Array removed) include:

- Treatment resistant (serious) infection at the implantation site or Patient pedestal
- Array technical malfunction resulting in an inability to collect data that is useful

for brain-control tasks

- Serious medical complications that compromise the subject's safety or health
- Psychological distress associated with decrements in performance or continued implantation.

If the participant is non-compliant (e.g., unwilling to participate in BMI training sessions) they may be withdrawn from the study. The NeuroPort Arrays will be explanted and they will be strongly encouraged to attend the follow-up monitoring visit with the study neurosurgeon.

3.4.5 Schedule of activities (Study Table):

The schedule of activities remains the same as in Table 1, Section 2.4.5, except that the implantation duration and all affiliated procedures (BMI testing, psychological evaluations, clinical exams, etc.) may be extended for up to 5 years post-implant.

3.5 Study outcome evaluations

3.5.1 Study endpoints

The NeuroPort Arrays will be removed up to 5 years after implantation. A participant will be considered a success for safety if the device is not explanted for safety reasons during the 5 year post-implant evaluation. If the subject experiences treatment resistant (serious) adverse events, he or she will be withdrawn and the arrays will be explanted early (See Section E 3.4.4). The study may also end early if the subject is non-compliant (See Section E 3.4.4).

If the participant wishes to leave the NeuroPort Array implanted after 5 years, the participant will be counseled that they should have the NeuroPort Array removed and that not doing so could result in clinically significant adverse events. They will also be informed that brain-machine interface training will not continue. The consent form includes a statement that participants will be financially liable for any medical care resulting from complications of not having the device removed upon instruction of the study PI. We will however allow participants to have the device removed at anytime and the explantation costs would be covered by this study.

3.5.2 Sample size determination

This is the first study to evaluate a long-term implantation of microelectrode arrays in individuals with spinal cord injury (or other impairment resulting in upper limb paralysis). Because this is a feasibility study, we feel that it is appropriate to begin with a small sample size in this initial investigation. We are recruiting up to 5 participants for PRO10080021 and only these people would be eligible for the current study.

3.5.3 Outcome data and data analysis

Specific Aim 1a will be fulfilled through monthly clinical examinations as well as observations made by the research staff, participant, or their caregiver throughout the trial. Research staff will document volunteered and observed adverse events at least weekly during the BMI training sessions. Adverse events will be documented and reported to University of Pittsburgh IRB and to the FDA in accordance with the respective reporting requirements and in the annual report. This documentation will serve as documentation of the safety of device in this small sample.

Specific Aim 1b is to characterize signal quality (firing rate, number of units recorded) over the duration of implantation. Data to support this aim will be collected at least weekly during the BMI training sessions. Our primary method of analysis will be to plot the trends in signal quality measures over time. The trend will be quantified using regression techniques.

Specific Aim 2 is to demonstrate that individuals with tetraplegia can learn to successfully control of a variety of external devices and computer-driven tasks using signals recorded with the NeuroPort Array. In additional to video documentation of brain-controlled device operation, we will quantify the number of degrees of freedom achieved by each participant at regular intervals for the duration of implantation. Multiple baselines will be defined as the level of computer assist will decrease with training. We will use regression to quantify changes in performance at a given assist level. Similarly, trends in success rate and computer assist level for a given task will be quantified over the duration of the trial using regression.

Specific Aim 3: Source localization (combining the MEG and structural MRI data) will be used to identify the anatomical foci of cortical activation controlling imagined and/or attempted movement. The coordinates (x,y,z) of the center of activation can be computed with fMRI or MEG relative to the head coordinate system defined using bony landmarks. The location and area of cortical activation measured by fMRI and MEG during imagined and/or attempted movement will be compared for each subject. A paired t-test will be used to compare location and area of cortical activation measured by the two imaging techniques using data from all participants, although the power of this test may be limited by sample size. Qualitative comparisons will be informative and we expect agreement between the two imaging techniques in terms of localizing the area for array implantation. MEG potentially offers additional information due to higher temporal resolution.

Specific Aim 3a: Cortical modulation will be calculated as the power of the 4-40 Hz frequency band of MEG data that is recorded during imagined and/or attempted movement. Specific Aim 3a will be evaluated by applying repeated measures ANOVA to test for differences in modulation (magnitude and total area) during imagined and/or attempted movement during the pre-surgical procedures and the follow-up sessions.

Specific Aim 4: Sleep quality measures will be correlated to BMI performance on the following day while controlling for differences in task difficulty. Linear regression will be used to determine the most predictive sleep quality metrics.

The study will be considered a success if the device is not explanted for safety reasons during the 12-month to 5 year post-implant evaluation. This study is not being proposed to support marketing applications (510(k) or PMA) for the NeuroPort Arrays. Instead, the goal is to demonstrate that three-dimensional microelectrode arrays provide a safe way to record sufficient neural information for controlling complex assistive devices that will increase the independence of individuals with disabilities.

3.5.4 Data and Safety Monitoring Committee

The independent Data and Safety Monitoring Board (DSMB) that oversees the core study, will also oversee the extension study following the procedures described in section 2.5.4. Similarly, the core members of the research team will meet at least monthly to provide additional internal study monitoring as for the core study. We will comply with the IRB's policy for the reporting of serious and unexpected adverse events as described in Chapter 3.0 of the University of Pittsburgh's IRB Reference Manual. Similarly, we will report adverse device events to the FDA in accordance with the agency's expedited reporting requirements.

4.0 Risk Analysis

For each risk, we have noted whether it is applicable to the core study, extension study, or both.

4.1 Anticipated risks

This study involves potentially serious risks. The risks of all experimental procedures are described below along with the steps that will be taken to minimize those risks.

<u>Risks Common to all Study-Related Activities (Core Study and Extension Study)</u>

There is a risk of breach of confidentiality since personal information will be obtained.

Some of the research activities may require the participant to transfer out of their wheelchair such as the MRI, CT, MEG, and x-ray. There is a risk of falling during the transfer.

There is also a risk of pressure sores with any prolonged sedentary activity for individuals with compromised nervous systems, such as those with SCI. This risk is not unique to participating in this study, and it is a common risk for prolonged sitting (e.g. in wheelchairs). This includes imaging sessions (MRI, CT, MEG, and x-ray) as well as BMI training/testing.

Some of the research procedures involve radiation exposure including the pre-operative

chest x-ray, and post-operative head CT and x-ray. The exposure for each procedure is specified below, but the expected total radiation exposure to the head is expected to be 2.6-5.6 rems. More imaging studies may be necessitated by the participant's medical condition. For reference, an annual radiation exposure of 20 rems is permitted to the most sensitive organs of radiation workers by federal regulations. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer.

Steps taken to minimize these risks:

Identifiable data will be filed in locked areas immediately after collection. Study ID numbers will be used instead of the participant's name when recording study-related data. The information collected in this study, such as neural recordings, will generally consist of numbers with little or no meaning to the casual observer. Electronic data is stored on password-protected network drives. Staff has been trained regarding the critical nature of participants' privacy, and about the procedures for respecting their privacy and maintaining confidentiality.

The research staff will be trained to assist participants with transfers as well as to perform dependent transfers. If the participant can transfer independently, they will be spotted. Assistive devices (e.g. sliding board or hoyer lift) will be available as necessary.

We will exclude individuals with a recent history of pressure sores from this study. The risk of developing a pressure sore is infrequent and can be significantly reduced by frequent change of sitting position, pressure relief movement, and usage of cushion. The duration of the imaging sessions that require the participants to remain still will be minimized. We will encourage participants to follow their normal pressure relief routines during experimental sessions.

The imaging studies are required to ensure the participant's safety both pre-operatively and post-operatively. The risk associated with the amount of radiation exposure that the subject will receive from this additional x-ray exam is considered to be low and comparable to everyday risks.

<u>Risks of the Screening Interview Neuropsychological Examination, and Post-Operative Visit with Rehabilitation Psychologist (Core Study)</u>

There is a risk of breach of confidentiality as personal information will be recorded.

Steps taken to minimize this risk:

A screening script will be used to determine whether the subject meets the inclusion/exclusion criteria. This information will be recorded using a coded subject ID. If it is determined that the subject is not eligible or does not wish to participate, this information will be destroyed.

Information from the neuropsychological examination will be recorded using a coded

subject ID. If it is determined that the subject is not eligible or does not wish to participate, this information will be destroyed.

Risks of fMRI (Core Study)

MRI is widely used in clinical practice, and the risks of MRI are believed to be very low. There is no ionizing radiation exposure involved and the studies are non-invasive. The magnet will make intermittent, loud, knocking noises that could cause ear discomfort in some people. Also, the rapidly switched magnetic fields used during imaging may cause nerve stimulation (e.g., an uncontrolled twitch or tickle near the waist). It is possible that the subject may experience feelings of anxiety or claustrophobia during the MRI scans. There is also a risk of the MRI scanner attracting metal objects.

Steps taken to minimize these risks:

Steps will be taken to minimize potential discomforts due to noise in the fMRI, such as wearing earplugs and informing the subject about the procedures. Two-way communication will be maintained at all times in case the subject experiences feelings of anxiety or claustrophobia.

The fMRI scanner may attract metal objects. Metallic implants, pacemakers, and other metallic substances are considered contraindications for MRI and therefore would exclude someone from participating in this study. It is possible to use a MRI-compatible ventilator for someone who is normally ventilator-dependent. Therefore this would not exclude someone from participating in this study. The Magnetic Resonance Research Center will also perform their standard screening procedures prior to the scan to ensure the subject's safety.

Risks of Blood Draw for Pre-Operative Screening (Core Study and Extension Study)

The insertion of the needle to draw blood may cause temporary discomfort, bruising from where the needle enters the vein, or soreness. These risks related to the blood draw are anticipated to be common, or expected to occur in 10% or greater of the participants (10 or more out of 100 people).

There is a slight risk of infection. Fainting may occur, but this risk is expected to be rare, or occur in less than 1% of people, or less than 1 out of 100 people.

Steps taken to minimize these risks:

Pre-operative screening will be performed at the Anesthesia Pre-Op clinic which routinely performs this evaluation for neurosurgical candidates. This screening is necessary to ensure that the participants are not at increased risk for complications during surgical procedures.

Risks of Chest X-ray for Pre-Operative Screening (Core Study and Extension Study)

The maximum amount of radiation exposure that participants will receive from the x-ray

exam is approximately 0.3 rem (a unit of radiation exposure) to the area of the body evaluated with minimal exposure of other areas of your body. For comparison, this is a small fraction (1-2%) of the annual radiation exposure (20 rems) permitted to the most sensitive organs of radiation workers by federal regulations. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive from this additional x-ray exam is considered to be low and comparable to everyday risks.

Steps taken to minimize these risks:

Pre-operative screening will be performed at the Anesthesia Pre-Op clinic which routinely performs this evaluation for neurosurgical candidates. This helps assure minimal radiation exposure and good technique for acquiring the film. This screening is necessary to ensure that the participants are not at increased risk for complications during surgical procedures.

Risks of EKG for pre-operative screening (Core Study and Extension Study)

There is a risk of skin irritation after removal of the electrodes used for EKG monitoring.

Steps taken to minimize these risks:

Pre-operative screening will be performed at the Anesthesia Pre-Op clinic by personnel who are trained to perform EKG screening. Cleaning the skin after removal of the electrodes will reduce the risk of skin irritation.

Risks of Structural MRI with IV Contrast (Core Study)

MRI is widely used in clinical practice, and the risks of MRI are believed to be very low. There is no ionizing radiation exposure involved and the studies are non-invasive. The magnet will make intermittent, loud, knocking noises that could cause ear discomfort in some people. Also, the rapidly switched magnetic fields used during imaging may cause nerve stimulation (e.g., an uncontrolled twitch or tickle near the waist). It is possible that the subject may experience feelings of anxiety or claustrophobia during the MRI scans. There is also a risk of the MRI scanner attracting metal objects. The contrast agent is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly. There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle (small plastic tube) to inject the gadolinium may cause minor pain, bruising and/or infection at the injection site. People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased

movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung. NSF/NFD is a serious progressive disease and can result in death. If the subject has severe kidney failure and receives gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check kidney function before gadolinium contrast is injected.

Steps taken to minimize these risks:

Steps will be taken to minimize potential discomforts due to noise, such as wearing earplugs and informing the subject about the procedures. Two-way communication will be maintained at all times in case the subject experiences feelings of anxiety or claustrophobia.

The MRI scanner may attract metal objects. Metallic implants, pacemakers, and other metallic substances are considered contraindications for MRI and therefore would exclude someone from participating in this study. It is possible to use a MRI-compatible ventilator for someone who is normally ventilator-dependent. Therefore this would not exclude someone from participating in this study. The Magnetic Resonance Research Center will also perform their standard screening procedures prior to the scan to ensure the subject's safety.

Participants will be asked to notify a doctor, nurse or technologist if they are allergic to gadolinium, if they have any kidney problems, or if they experience any of these or other side effects. Individuals with renal failure or dysfunction will be excluded from study participation. A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Risks of MEG Testing (Core Study and Extension Study)

MEG testing has minimal risks. The MEG system records brain activity non-invasively. It does not require implantation of electrodes in the brain or the application of electrodes to the scalp. MEG recording will be conducted with an FDA-approved MEG system (Neuromag®) located in the MEG Center at University of Pittsburgh Medical Center (UPMC). This facility is also used routinely for clinical diagnostics, and the MEG system is well-maintained to be used safely on humans. During experiments, participants will sit in a chair that is part of the MEG system with a comfortable posture. Participants will be asked to keep still during MEG recording and they may become fatigued during the session since long periods of concentration may be required. It is also possible that the subject may experience feelings of anxiety or claustrophobia during MEG testing.

Steps taken to minimize these risks:

We will have a seat belt available to help with postural support and will have the option to conduct the MEG while the participant is in a supine position if necessary. Rest breaks will be incorporated throughout the testing session to minimize the risk of fatigue. We will encourage participants to perform frequent pressure relief movements and will provide a MEG-compatible cushion to reduce the risk of pressure sores. Two-way communication will be maintained at all times in case the subject experiences feelings of anxiety or claustrophobia.

Risks of Surgical Procedures (Core Study Implantation and Explantation and Extension Study Explantation Only)

In general, the surgical risks associated with implanting the NeuroPort Arrays are anticipated to be typical for any surgery for implanting a device in the brain. The risks should be similar to those for implanting a Deep Brain Stimulator (DBS). However, unlike a DBS implant, the NeuroPort Arrays are not implanted deep into the brain, but rather on the surface of the cortex. The risks associated with surgery include adverse reactions to surgical procedure, bleeding during surgery, infection post-surgery and potential tissue damage to the primary motor cortex during implantation of the NeuroPort Arrays. The risks associated with explantation surgery of the NeuroPort Array are similar to those during implantation surgery. Animal study data show that post-explantation, the primary motor cortex heals with no external signs of irreversible adverse effects. There is also a risk of developing a pressure sore during surgery for individuals with SCI.

There is a risk of bone resorption after the two surgeries where the bone flap is removed and replaced. The bone flap may breakdown and not heal properly however this risk is rare (<1%). If this occurs, the study neurosurgeon may perform an additional surgical procedure to replace the bone flap with an artificial material.

The subject will be under general anesthesia for the duration of the surgery. Minor risks of general anesthesia include nausea and vomiting (25%), sore throat (10-50%), post-operative pain (10-30%), headache (20%), drowsiness (50%), dizziness (20%), damage to the teeth or oral tissue (<1%), and peripheral nerve injuries (<0.3%). These risks are common but are typically temporary. Serious risks of general anesthesia, which are very rare (40), include: vision loss or blurriness (0.0008%), hearing loss (0.01%), anaphylaxis (allergic reaction, 0.01%), post-operative cognitive dysfunction (difficulty with concentration and memory, 1% for individuals over the age of 60), respiratory complications (0.03%), cerebrovascular accident (stroke, 1%), and cardiac arrest (<0.01%).

Autonomic hyperreflexia occurs during the life of up to 85% of patients with a complete spinal cord injury above T_5. This occurs due to excessive sympathetic response to stimuli below the level of injury, absent the brain's normal damping effect [50]. As a result, exaggerated hypertensive responses can be expected due to surgical stimuli that can be properly blocked by deep anesthesia, or vasoactive agents. In a large case series (n=271 individuals with SCI at T_5 or higher), 16% of patients experienced mild or severe autonomic hyperreflexia in the presence of anesthesia [51]. However, all but ten of these

cases involved urological procedures. Since the current study involves a neurosurgical procedure, the stimuli will be above the level of the lesion and therefore the risk of hyperreflexia is reduced. Also, in response to hypertensive episodes, significant bradycardia can occur due to unopposed parasympathetic cardiac tone that can be treated with vasoactive agents.

Patients with chronic SCI also have a risk of deficient body temperature regulation due to loss of supraspinal regulation requiring meticulous management of hypothermia. An additional anesthesia-related risk in chronic SCI patients is an increased incidence of atelectasis postoperatively due to respiratory muscle compromise requiring extended controlled or assisted ventilation and chest physiotherapy, as well as postural drainage. Based on the literature and our experience, we believe the risks of anesthesia that are specific to SCI to be infrequent (1-10%).

After a neurosurgical procedure, common minor risks include mild to moderate headache, eyelid swelling, bruising around the eye, minor swelling of the incision, and minor CSF leaks that are easily stopped [52]. These risks are common to implantation and explantation of the device.

Steps taken to minimize these risks:

Participants will undergo pre-operative labs and screening at the Pre-Op Anesthesia Clinic to ensure that they are not deemed to have an increased surgical risk beyond the increased risk that is associated with spinal cord injury or other neurological disease/condition.

The director of Neuroanesthesiology at UPMC will oversee anesthesia care for participants in this study to ensure that participants are monitored adequately to allow for rapid intervention. As an additional layer of protection for responding to autonomic hyperreflexia, an A-line (intra-arterial catheter) will be inserted to allow for rapid intervention if necessary. In order to minimize autonomic hyperreflexia-related risk, participants with cardiovascular disease and coagulopathies (identified by pre-operative screening) will be excluded from this study.

We will follow the standard clinical procedures to minimize the risks associated with surgical implantation or removal of electrodes. For example, antibiotic prophylaxis administration is usually initiated for the patient approximately two hours before the surgery and will be maintained as directed by the study neurosurgeon and their clinical team. We have excluded pregnant females and those with renal failure as they may be at an increased risk for complications resulting from administration of the antibiotics. Complications or side effects usually result from prolonged dosing, rather than the single dosing that will be administered in this study. Antibiotic ointment and sterile dressings will be applied to the implantation site to minimize the risk of infection. Standard sterile surgical techniques will be followed for this study. This includes sterilization of the NeuroPort Arrays before the surgery and proper handling of NeuroPort Arrays during the surgery. The Patient Pedestals will be covered with antibiotic ointment and sterile dressings. These procedures will greatly

minimize the risk of infection. The NeuroPort Arrays will be placed away from blood vessels to minimize the risk of bleeding/bruising. Sufficient padding will be used to reduce the risk of pressure sores during surgery and individuals with a recent history of pressure sores will be excluded from participation.

Risks of Chronic Recording with NeuroPort Arrays (Core Study and Extension Study)

The primary risks of chronic recording center around the long-term presence of the NeuroPort Arrays and Patient Pedestals. The risks associated with the chronic implantation of the NeuroPort Arrays are expected to be similar to those observed with the implantation of other chronic devices such as deep brain stimulators and cochlear implants. Some of these include, but are not limited to thrombosis, embolism, body rejection phenomena, neurological complications, and infection (meningitis and cellulites) (see full list below). The most common complication for these types of devices is infection. Infection rates for other implanted devices requiring a craniotomy range from 4 to 12% [20-22]. The outcome of infection may be serious and may lead to brain edema or other sequelae. If the infection cannot be treated with antibiotics, the NeuroPort Arrays may need to be explanted. Some of these procedures included in the infection risk estimate are more invasive than that proposed in the current study. Because we will perform a smaller craniotomy with a wound closure away from the implantation site, and due to the lack of clinical adverse events observed in the BrainGate trial, we believe that the risk of infection for a single NeuroPort Array is at the low end of this range (approximately 5-6%). Based on our team's experience with other neurosurgical procedures, we estimate the elevated risk of infection due to the presence of two percutaneous Patient Pedestals to be less than 50% of the current risk. Therefore the expected risk of infection for the proposed study is approximated to be less than 9%. Most of the risk for infection is due to environmental factors in the operating room and therefore having two percutaneous sites only introduces an incremental increase in the risk of infection.

There is also the potential for seizure and other neurological sequelae due to the presence of a chronic implant in the brain. It is possible that a subject that has limited ability to move finger(s) may lose that ability due to implant of the NeuroPort Array. It is unlikely that local tissue damage resulting from the inflammatory response will lead to functional deficits. No such deficits have been reported in any of the previous animal or human studies. As a point of reference multiple subpial transections, in which a series of shallow cuts are made into the cortex, are performed for treatment of intractable epilepsy where the seizure foci are located in areas of the brain that cannot be removed safely, such as the motor cortex. Major complications with this type of procedure are rare and neurological deficits appear to be only temporary [25, 26]. While unexpected, if any serious adverse events occur and they are resistant to treatment, the PI will recommend to the subject that the NeuroPort Array be explanted. Subjects will be followed for at least three weeks post-explant, and longer, if clinically necessary.

Based on published literature, and our plan for continued wound care and clinical monitoring, we do not believe that extending the implantation duration increases the risks of chronic implantation.

Table 2 summarizes possible risks, along with a brief definition, that may occur due to implantation and chronic recording with NeuroPort Arrays. Due to the limited number of human studies with the NeuroPort Arrays, it is difficult to provide quantitative estimates for each possible risk. However, based on published reports and discussions with BrainGate investigators, we expect the risk of serious or chronic adverse events to be very low. Based on our experience with other common neurosurgical procedures (such as deep brain stimulation and electrocorticography monitoring), we have provided our best estimate of the expected rate of occurrence for each clinical event.

Table 2. Possible risks of chronic implantation of the NeuroPort Array

Risk	**Definition**	**Rate of Occurrence** Rare: <1% Infrequent: 1-10% Common: >10%
Additional paralysis	Permanent or temporary loss or impairment of the subject's ability to move a body part	Rare
Adverse reaction to anesthesia	Reaction to any anesthetic agent given	Rare
Allergic reaction	Hypersensitivity reaction to a particular allergen	Infrequent
Ataxia of neck and facial muscles	Loss of the ability to coordinate muscular movement of the neck and facial muscles	Rare
Attention deficit	A deficiency or impairment in ability of the subject to concentrate	Rare
Autonomic dysreflexia	Paroxysmal rises in blood pressure	Rare
Bald spot	Lacking hair	Common
Blood clot	Blood clot (near surgical site)	Infrequent
Cognitive deficit	A permanent or temporary deficiency or impairment in mental functioning	Rare
Cramping	A sudden, involuntary, spasmodic muscular contraction causing severe pain, often occurring in the leg or shoulder as the result of strain or chill	Rare
Death	Subject death	Rare
Diplopia	A disorder of vision in which a single object appears double	Rare
Disequilibrium	Loss or lack of stability or equilibrium	Infrequent
Dizziness/vertigo	Having a whirling sensation and a tendency to fall	Infrequent
Dysarthria	A disturbance of speech due to emotional stress, to brain injury, or to paralysis, in coordination or spasticity of the muscles	Rare
Dysphagia	Difficulty in swallowing	Infrequent

Encephalitis	Inflammation of the brain	Rare
Epidural hematoma	A localized swelling filled with blood resulting from a break in a blood vessel located on or over the dura mater	Rare
Erosion around lead or pedestal	An eating or gnawing away of the tissue around the pedestal	Infrequent
Erythema along lead tunnel or pedestal	Redness of the skin caused by dilatation and congestion of the capillaries	Common
Exacerbation of underlying motor deficit	Temporary aggravation of the preexisting basic or fundamental motor deficit	Infrequent
Facial paresis	Paralysis of the face	Rare
Fatigue	Temporary physical or mental weariness resulting from exertion	Common
Fever	Abnormally high body temperature	Infrequent
Hemorrhage	Excessive discharge of blood from the blood vessels; profuse bleeding	Rare
Headache	A pain in the head	Common
Histotoxic reaction	The chronically implanted components have a poisonous effect on the tissues	Rare
Hoarseness	Having or characterized by a husky, grating voice	Infrequent
Hypersensitivity to Chlorhexidine	Highly or excessively sensitive to chlorhexidine	Infrequent
Immune rejection	The failure of the body to accept implanted material as a result of immunological incompatibility; immunological resistance to foreign material	Rare
Incision site pain	Temporary pain along the cut made during surgery	Common
Infection	Invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms. One type of infection is cellulitis or insertion site skin infection	Infrequent
Inflammatory process	A protective tissue response to injury or destruction of tissues	Infrequent
Intraparenchymal hemorrhage	Excessive discharge of blood from the blood vessels; profuse bleeding occurring within the parenchyma	Rare
Lead migration	A spontaneous change in the place of the lead	Rare
Loss of residual movements	Loss of any movements that the subject had prior to the surgery	Rare
Meningitis	Inflammation of the meninges of the brain and the spinal cord, most often caused by a bacterial or viral infection and characterized by	Rare

	fever, vomiting, intense headache, and stiff neck	
Nausea	Nausea	Common
Neck dystonia	Abnormal tonicity of muscle, characterized by prolonged, repetitive muscle contractions that may cause twisting or jerking movements of the neck	Rare
Neck pain	An unpleasant sensation occurring in varying degrees of severity as a consequence of injury or disease in the neck	Rare
Neck paresis	Paralysis of the neck	Rare
Neurological deficits	A permanent or temporary deficiency or impairment in neurological functioning	Infrequent
Non healing wound	A wound that because of infection or disease will not close with granulation tissue	Rare
Numbness	Deprived of the power to feel normally	Rare
Pedestal site drainage	Fluid leaving the pedestal site	Rare
Pedestal site ecchymosis	The passage of blood from ruptured blood vessels into subcutaneous tissue, marked by a purple discoloration of the skin	Common
Pedestal site pain	An unpleasant sensation occurring in varying degrees of severity as a consequence of injury or disease	Infrequent
Percutaneous site infection	Invasion by and multiplication of pathogenic microorganisms in the area of the pedestal	Infrequent
Perioperative bleeding	Bleeding during surgery	Rare
Post-operative bleeding	Bleeding after surgery	Rare
Psychiatric episode	Mental and emotional disorder of brief duration	Infrequent
Scalp necrosis	Scalp tissue that dies	Rare
Scalp numbness	Deprived of the power to feel the scalp	Common
Scarring	Scar at site of implant/explant	Common
Seizure	A sudden attack, spasm, or convulsion, as in epilepsy or another disorder	Infrequent
Sensor migration	Sensor moves outside the primary motor cortex	Rare
Skin inflammation	A localized protective reaction of skin to irritation, injury, or infection, characterized by pain, redness and swelling	Common
Skin irritation	A condition of inflammation, soreness, or irritability of the skin	Common
Spasticity	A state of increased tone of a muscle	Rare
Speech deficits	A deficiency or impairment in mental or physical function of speech	Rare
Stroke	Sudden loss of brain function caused by a blockage or rupture of a blood vessel to the	Rare

	brain, characterized by loss of muscular control, diminution or loss of sensation or consciousness, dizziness, slurred speech, or other symptoms that vary with the extent and severity of the damage to the brain	
Subarachnoid hemorrhage	Excessive discharge of blood from the blood vessels; profuse bleeding occurring beneath the arachnoid membrane	Rare
Subdural hematoma	A localized swelling filled with blood resulting from a break in a blood vessel located or occurring beneath the dura mater	Rare
Tissue granulation	Small, fleshy, beadlike protuberances, consisting of outgrowths of new capillaries, on the surface of a wound that is healing	Common
Wound healing difficulties	Occurs when wound does not heal as expected or within expected time frame	Infrequent
Vocal cord paresis	Paralysis of the vocal cord	Rare

Steps taken to minimize these risks:

Several steps have been taken to mitigate potential risks associated with the NeuroPort Arrays. By design, the NeuroPort Arrays have a small profile to minimize impact to the cortex tissue and thereby reduce bleeding following insertion. This means that a relatively small craniotomy can be made in comparison to other procedures such as invasive epilepsy monitoring.

To minimize tissue damage at the site of implantation, a pneumatic Array Inserter tool which standardizes the implantation of the NeuroPort Array, will be provided. The tool inserts the Sensor at a specific rate and is designed to cause minimal tissue damage. Animal studies of the NeuroPort Array have shown little or no tissue damage at the implantation site. Due to the subject's preexisting condition this area of the brain has been essentially disconnected from communicating with other parts of the body. So, the visible effects directly related to potential injury to the primary motor cortex tissue are expected to be insignificant and are not anticipated to compromise the subject's medical or neurological baseline status.

The device materials in contact with the body are known biocompatible materials. Animal study results of the NeuroPort Array reveal an absence of, or a limited observed, systemic toxic effects or adverse neurological effects.

Because the pedestal protrudes through the skin, there is a risk of infection even after surgical healing and recovery. The risks of the long-term presence of the Patient Pedestal are minimized by an infectious disease screen, frequent checks performed by a caregiver, and a specific wound/skin care procedure designed to reduce the chance of infection. The protocol describes steps taken before and during surgery to create a sterile environment and to exclude individuals who may be at high risk for infection. Participants will also undergo immediate post-operative care in the neurosurgical

ICU, neurosurgical medical surgery recovery unit, and the UPMC Rehabilitation Institute. During ongoing device use, a family member or caregiver will be instructed to inspect the Patient Pedestal site daily. The Patient Pedestal will be cleaned at least every 7 days. Also, we will monitor the subject's temperature each day when BMI training occurs since this is a reliable indicator of infection. The subject will also be instructed to monitor and record their temperature daily. This will allow us to provide appropriate clinical care in a timely manner.

Risk of Fibrosis due to Chronic Implantation (Core Study and Extension Study)

There is a risk that it may not be possible to remove one or both of the arrays due to fibrosis (excessive tissue growth). We believe that it is very unlikely (<1%) that this will occur. If the risk of damage to the cortex outweighs the priority to remove the Arrays, our surgeon sub-investigator would cut the lead wire and remove the pedestal(s) leaving the 4 x 4 mm array(s) implanted. The risk of migration would be minimal since the array would be encased in the fibrous tissue. It is possible that the participant may not be able to have an MRI if the array(s) remains implanted since MR safety guidelines differ between institutions. The procedure for evaluation would be similar to other devices that remain implanted near the brain such as titanium plates, metal (aneurysm) clips, and silastic catheters. We do not expect that additional follow-up, beyond the 2 planned visits (1 and 4 weeks post explant) with the neurosurgical team, will be required. We do not believe that extending the implantation duration for up to 5 years increases the risk of fibrosis that would make it more difficult to remove the array.

Steps taken to minimize these risks:

The neurosurgeon sub-investigator will evaluate the extent of fibrosis prior to removing the arrays and determine whether they can be removed safely. The neurosurgeon sub-investigator is board-certified and experienced in removal of implanted devices. Based on our experience with non-human primate research at the University of Pittsburgh and the published results of the human BrainGate trials, we believe that the risk of having to leave the arrays implanted is very low (<1%).

Risks of Post-Operative Head CT (Computed Tomography) (Core Study)

The amount of radiation exposure that participants will receive from the head CT is approximately 2-5 rems (a unit of radiation exposure) to the area of the body evaluated with minimal exposure of other areas of your body. For comparison, this is a small fraction (<25%) of the annual radiation exposure (20 rems) permitted to the most sensitive organs of radiation workers by federal regulations. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive from this study is considered to be low. A head CT will only be conducted as part of the extension study if ordered by the neurosurgeon to investigate a change in the participant's neurological status.

Steps taken to minimize these risks:

It is standard clinical procedure to perform a head CT after a neurosurgical procedure in which electrodes are implanted. This allows for documentation of electrode location and can identify possible adverse reactions (such as bleeding or swelling) following surgery. The risk associated with the amount of radiation exposure that the subject will receive from this exam is considered to be low and comparable to everyday risks.

Risks of Post-Operative Head X-ray (Core Study)

The maximum amount of radiation exposure that participants will receive from the x-ray exam is approximately 0.3 rem (a unit of radiation exposure) to the area of the body evaluated with minimal exposure of other areas of your body. For comparison, this is a small fraction (1-2%) of the annual radiation exposure (20 rems) permitted to the most sensitive organs of radiation workers by federal regulations. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that the subject will receive from this additional x-ray exam is considered to be low and comparable to everyday risks. A head x-ray will only be conducted as part of the extension study if ordered by the neurosurgeon to investigate a change in the participant's neurological status.

Steps taken to minimize these risks:

It is standard clinical procedure to perform a head x-ray after a neurosurgical procedure in which electrodes are implanted. This allows for documentation of electrode location. The risk associated with the amount of radiation exposure that the subject will receive from this exam is considered to be low and comparable to everyday risks.

Risks of BMI Training/Testing (Core Study and Extension Sudy)

During training, subjects will be asked to perform simple tasks that carry no risk above what is experienced during a typical daily routine. Subjects will perform simple movements or learn to control computer cursors or virtual objects. The research personnel will ensure that the behavioral tasks and their difficulty levels are set properly for each subject. We may ask them to attempt to control a prosthetic limb or robotic arm. Risks from interaction with the prosthetic or robotic arm or from dropping objects being transported by the arm include potential bruises or abrasions or minor damage to the participant's wheelchair. The risk of these is infrequent (1-10%) and precautions will be taken to minimize this risk. We may ask them to attempt to control a robotic arm exoskeleton (Figure 5). Risks from interaction with the exoskeleton arm would include possible injury to subject's arm if it moves past a comfortable joint position or if it collides with wheelchair or other parts of subject's body.

We may attach additional skin electrodes to record EMG or provide a ground for our BMI system. These electrodes are commonly used for this type of recording, but they may cause minor skin irritation. Also, we may stimulate peripheral nerves as part of our somatosensory testing which may cause discomfort or spasticity in some subjects. This testing can be stopped at any time.

In addition to physical risk, there is a psychological risk to participation in BMI training sessions. Individuals may experience frustration during the training, particularly early in the study. During the extension study, participants may experience frustration as signal quality starts to decline. Participants may have feelings of negativity or other emotional concerns during the study.

Steps taken to minimize these risks:

During training, subjects will be asked to perform simple tasks that carry no risk above what is experienced during a typical daily routine. The research personnel will ensure that the behavioral tasks and their difficulty levels are set properly for each subject. Testing can be stopped at any time and we will work with the subject to determine session start time and duration. Investigators will be present during all testing sessions to ensure safe operation of any external devices that are used. Safe operation will be ensured in a variety of ways including manual override control by the operator, slow operation speed of the device, and defined workspaces that prohibit contact between the participant and the technology.

In order to avoid risks from close proximity with the prosthetic or robotic arm or robotic arm exoskeleton, the following precautions are in place: (1) ensuring the subject has demonstrated adequate brain control of the robotic arm when positioned at a safe distance away from the participant (judged by the sponsor/investigator, likely >75% success on simple reaching tasks), (2) ability to program the robotic arm or exoskeleton with appropriate workspace and/or range-of-motion limits and definitions, and (3) constant monitoring of interaction with the robotic arm or exoskeleton by the study team who have the ability to stop the robotic arm via computer control or manual power shut-off.

Figure 5: Robotic Arms: Modular Prosthetic Limb (LEFT) and ArmeoPower exoskeleton (RIGHT)

Since BMI testing requires frequent sessions and significant effort on the part of the participant, older participants may become easily fatigued and therefore we have limited our age group to 18-70 years. Additionally, frequent training is necessary to induce neuroplasticity and we believe it may be more difficult to induce neuroplasticity in older individuals.

Individuals may experience frustration during BMI training sessions, particularly early in the study. For the extension study, participants will be informed that it is likely that signal quality will degrade over time. This may make it more difficult to complete the tasks so the difficulty and complexity may need to be reduced. Participants can be scheduled for appointments to speak with a psychologist throughout the study (approximately 1, 3, 6 and 9 months after implantation and again prior to explantation) to discuss any concerns they have during the study. The visits will occur every 3 months during the extension study as well. In addition, physician-investigators may refer the subjects to additional psychological appointments at their discretion.

Risks of EEG/EKG Recording (Extension Sudy)

Minor skin irritation may develop from the placement and removal of EKG and EEG electrodes.

Steps taken to minimize these risks:

Cleaning the skin after removal of the electrodes will reduce the risk of skin irritation. If skin irritation does occur, an over-the-counter ointment can remedy this.

Risks of In-Home Sleep Evaluation (Extension Sudy)

Participant may experience fatigue following sleep evaluation, if amount of sleep was insufficient or below normal amount.

Steps taken to minimize these risks:

Participant and caregiver will be asked to ensure that participant does not perform any activities that would invite risk of injury until the fatigue has subsided..

Risks of Pregnancy (Core Study and Extension Study)

Women who are, or plan to become, pregnant are excluded from the study due to potential risks to the unborn fetus or themselves. These risks include radiation exposure during x-ray or CT imaging which may lead to birth defects, mental impairment, cancer, or miscarriage. There are no known risks associated with undergoing an MRI scan while pregnant and the risks of MRI to the fetus are felt to be very small, but are nevertheless also not known. Any complications during surgery would put the fetus at risk for distress. We do not believe that pregnancy would carry any additional risks while the array is implanted, however this has not been studied and therefore the risks are unknown.

Steps taken to minimize these risks:

Study investigators will discuss the risks of pregnancy during the course of the study and will advise women against becoming pregnant. Women will be advised to notify the study team immediately if they learn they are pregnant.

4.2 Adverse event recording/reporting

4.2.1 Adverse event definitions

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

Serious adverse effect. Any adverse effect 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 effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

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

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

4.2.2 Eliciting adverse effect information

Study subjects will be routinely questioned about adverse effects at study visits.

4.2.3 Recording and assessment of adverse effects

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

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

4.2.3.1 Abnormal test findings

An abnormal test finding will be classified as an adverse effect 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 effect.)
- The test finding leads to discontinuation of subject participation in the clinical study.
- The test finding is considered an adverse effect by the investigator-sponsor.

4.2.3.2 Causality and severity assessment

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

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

4.2.4 Reporting adverse effects to the FDA

The investigator-sponsor will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. 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 investigator-sponsor first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the investigator-sponsor 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 that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

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

4.2.5 Reporting of adverse effects to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect 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 effect; and 3) an unexpected adverse effect. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 5 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects 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 investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects 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 effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

Adverse events will also be summarized in reports to the DSMB. Any events related to wound infections, scalp or skull breakdown, or other local wound issues will be reported to the DSMB Chairperson within 24 hours.

4.3 Withdrawal of subjects due to adverse effects

The subject will be under medical supervision for the duration of this study. Their health will be the top priority and participation will be discontinued if an intervention is required. The study neurosurgeon and PI will be primarily responsible for evaluating the subject's condition. Complications that could result in removal from the study (and having the NeuroPort Array removed) include:

- Treatment resistant (serious) infection at the implantation site or Patient pedestal
- Array technical malfunction resulting in an inability to collect data that is useful for brain-control tasks
- Serious medical complications that compromise the subject's safety or health

5.0 Monitoring Procedures

Independent monitoring of the clinical study for clinical protocol and IDE application compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the University of Pittsburgh's Education and Compliance Office – Human Subject Research (ECO-HSR). The address of the ECO-HSR is listed below. Monitoring procedures of the ECO-HSR are listed on its website at http://www.rcco.pitt.edu/educ/.

Education and Compliance Office – Human Subject Research
Research Conduct and Compliance Office
University of Pittsburgh
Hieber Building, Suite 205
3500 Fifth Avenue
Pittsburgh, PA 15213

The investigator-sponsor and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data. Representatives from the Department of the Navy Human Research Protection Program may also provide study oversight and monitoring as part of their responsibility to protect human research subject volunteers.

6.0 Labeling

Refer to section K. of the IDE application.

7.0 Consent Materials

Refer to section L. of the IDE application.

8.0 IRB Information

Refer to section H. of the IDE application.

9.0 Other Institutions

Refer to section I. of the IDE application.

10.0 Additional Records and Reports

10.1 Data handling and record-keeping

Case Report Forms (CRFs) will be completed for each subject enrolled into the clinical study. CRFs are included in Appendix I. CRFs will be signed by the principal investigator or a qualified sub-investigator as indicated on each individual form. The principal investigator will sign a Case Report Verification Form prior to the implantation surgery, every month following implantation, and following explantation to verify that they have reviewed all CRFs completed prior to the date of review. The investigator-sponsor's signature serves as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic. Any data that is missed will be noted with an explanation and investigator initials. Protocol deviations will be reported to the IRB as required.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the *Source Documents*. Whenever possible, Source Data for clinical research procedures will be stored as a print out of the electronic medical record note. CRFs will be used to document the key outcome variables for each procedure and will also indicate that all original data was stored and backed up as appropriate.

Paper-based records will be kept in a secure location in locked file cabinets within UPMC/University facilities. All researchers involved with the conduct of this research have been appropriately trained in the proper practices of research conduct. Each subject will be assigned a unique subject identification code and the link to that code will be stored on a restricted research server (described below). Whenever feasible, identifiers will be removed from study-related information and replaced by the subject identification code.

Photographing, videotaping, and/or voice-recording will be performed as part of this study and these data will be stored with study ID numbers in a locked office or on a password-protected research drive that can only be accessed by research staff only.

Electronic storage of research study information will be on a restricted access, separate server used only by PMR research faculty and staff. In order to maximize data security as well as our ability to analyze the data efficiently, we will utilize two research servers: (1) University of Pittsburgh Medical Center (UPMC) and (2) Rehabilitation

and Neural Engineering Laboratory (RNEL) on the University of Pittsburgh network. All identifiable information (excluding photographs, videotapes, and voice recordings) will be stored on the UPMC server. The UPMC server is managed by an information security group which is comprised of three main areas: threat and vulnerability management, identify management and account administration, and the technical team. Protection of information is maintained in a variety of ways including: firewall, individual password accounts, and identify management.

Due to the large file size of the research data, we plan to store deidentified data locally on the RNEL laboratory server. This server is password protected and only research personnel affiliated with this project will be able to access study-related data. All original data will be stored in a 'read only' folder and will also be backed up at a separate location either on DVD in a locked file cabinet or on a separate password-protected backup server. The case report forms related to electronic data collection will also document that the data was stored and backed-up appropriately. All case report forms will be verified by the principal investigator.

The neural data collected during BMI training is the primary data of interest for addressing the specific aims of this investigation. Data will be stored electronically on the local testing computer during each BMI testing session. At each session, a hard-copy log sheet will be completed by a research staff member that includes the coded subject ID, filenames, and task descriptions. Important parameters related to the participant (e.g. subject ID), task (e.g. target size and location, assist level, and task name) and session (e.g. date and time of data collection) are also saved within the structure. While all original data will be stored as 'read only', this provides extra protection that the data can always identified and/or linked to the log sheet using information stored within the structure. Deidentified neural data will be transferred from the local test computer to the research server and stored and backed up as described above.

Our study team will conduct regular reviews of ongoing data analysis to ensure the accuracy and validity of these methods. In no way will any of the original data be altered through these procedures. All case report forms, log sheets, and data and safety monitoring minutes will be made available to FDA or IRB representatives as requested.

All data will be kept for a minimum of 7 years after the study ends in compliance with the University of Pittsburgh guidelines. Collaborating investigators may have access to study data after they are de-identified.

10.2 Record maintenance and retention

The investigator-sponsor will maintain records in accordance with Good Clinical Practice guidelines to include:

- FDA correspondence related to the IDE application and Investigational Plan; including copies of submitted FDA Form 3500As, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition, and

failure to obtain informed consent reports;

- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements.
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;
- Curriculum vitae (investigator-sponsor and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for investigator-sponsor and listed sub-investigators;
- Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol);
- Signed informed consent forms;
- Completed Case Report Forms; signed and dated by investigator-sponsor;
- Source Documents or certified copies of Source Documents;
- Monitoring visit reports;
- Copies of investigator-sponsor correspondence to sub-investigators, including notifications of adverse effect information;
- Subject screening and enrollment logs;
- Subject identification code list;
- Investigational device accountability records, including documentation of device disposal; and the
- Final clinical study report.

Identifiable data will be filed in locked areas immediately after collection. Study ID numbers will be used instead of the participant's name when recording study-related data. The information collected in this study, such as neural recordings, will generally consist of numbers with little or no meaning to the casual observer. Electronic data is stored on password-protected network drives. Staff has been trained regarding the critical nature of participants' privacy, and about the procedures for respecting their privacy and maintaining confidentiality. Subject names and other directly identifiable information will not appear on any reports, publications or other disclosures of clinical study outcomes.

The investigator-sponsor will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational device; or, if a marketing application is not submitted or approved for the investigational device, until at least 2 years after investigations under the IDE have been discontinued and the FDA so notified.