CLINICAL PROTOCOL VERSION 7.0

TITLE OF STUDY:	Study of Treatment of Pain and Autonomic Dysreflexia by Deep Brain Stimulation in Participants with Spinal Cord Injury
DATE OF PROTOCOL:	June 30th , 2015
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1 CONTACTS

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2 PRINCIPAL INVESTIGATOR SIGNATURE

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study patients. Any supplemental information that may be added to this document is also confidential and proprietary to Sponsor and must be kept in confidence in the same manner as the contents of this protocol.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Principal Investigator's Signature

Jonathan R. Jagid
Principal Investigator's Name (Print)

07/01/2015
Date of Signature (DD/MMM/YYYY)

3 SYNOPSIS

Study Title	Phase 1 Study of Treatment of Pain and Autonomic Dysreflexia by Deep Brain Stimulation in Participants with Spinal Cord Injury
Study Rationale	Spinal cord injury (SCI) is a devastating disease, which exerts a disproportionate medical, social, and economic toll on society. Effective treatments are urgently needed for SCI, whether for immediate relief of symptoms or longer-lasting functional recovery. It (SCI) produces chronic loss of motor control, sensation and autonomic regulation below the level of the injury. Frequently disconnection is not total and some degree of below injury function remains. Unfortunately, the remaining functional connection can cause additional problems for patients (at least 20% of all SCI patients). In addition, dangerous rises in blood pressure can be produced by strong sensory input. This phenomenon is known as autonomic dysreflexia (AD). It occurs in 48% to 90% of patients with tetraplegia or high quadriplegia. This study investigates the neurosurgical procedure of deep brain stimulation (DBS) in the midbrain's periaqueductal and periventricular gray region (PAG/PVG). The use of DBS in PAG/PVG for drug-refractory non-metastatic chronic pain has been reported in the biomedical literature for at least several hundred patients, and continues to be used in many countries, including Germany and the United Kingdom. A small proportion of reported cases (about 21) of DBS applied at any brain site involved pain from spinal cord injury (SCI), and only 3 or 4 for the PAG/PVG. These reports, some of them from the 1970s, did not describe systematic studies. Extensive, modern pain testing was not done. The stimulation was not given time to work (it could require several weeks for effects to appear). The pathologies were in most cases inadequately characterized. Also, some preclinical evidence suggests PAG/PVG-DBS can also improve other SCI symptoms, such as motor deficits and autonomic dysreflexia (AD), which were never examined. The present study is designed to provide these missing details. Thus, our study seeks to examine whether the safety and efficacy of prolonged DBS for SCI are sufficient to warrant its larger-scale study as therapy for pain and AD in SCI patients.
Trial Design	• Controlled, open label, non-randomized, investigation in twelve (12) participants. • Two sites: (1) Miami Veterans Affairs Medical Center; (2) University of Miami Miller School of Medicine. • Informed Consent will be obtained prior to enrollment in the study.
Approximate Duration of Patient Participation	• 52 weeks (±7 days) for each subject from Initial Visit until Final Visit. • After implantation of the DBS device on the 8th week, scheduled safety and efficacy assessments will be performed at intervals of 4 weeks until study week 24, and at intervals of 8 weeks thereafter.

Approximate Duration of Study	• End of Study is Defined as Last Subject's Final Visit • Total period of study is 36 months, from when 1st subject enrolled.
Study Objective(s)	**Primary:** to determine whether Deep Brain Stimulation (DBS) applied bilaterally or unilaterally in the midbrain periaqueductal-periventricular gray (PAG/PVG) region provides acute or long-term relief of chronic SCI associated pain and autonomic dysreflexia. **Secondary:** to assess the clinical effects of DBS on autonomic functioning; to determine with Activa PC+S whether local field potentials in the PAG/PVG can be used to predict the efficacy of DBS in this region

Diagnosis and Main Criteria for Inclusion

Major Inclusion Criteria:

Inclusion Criteria	Measure	Rationale
Age ≥ 22	Years of age	Higher rates of neurological recovery if younger.
Age ≤ 60	Years of age	Different injury patterns and higher risk of complications if older
Level of injury at or above T12	Neurological exam	Eliminates injuries below thoracic level T12, which have different pain pattern

1. Neuropathic pain at or below the level of injury, as determined based on pain in an area with neurological deficit and described as burning, shooting, electric, stinging etc.
2. The injury must have occurred at least 1 year prior to entering the study and participants must have experienced chronic pain for a minimum of six months.
3. The disability must have a grade of on the American Spinal Injury Association Impairment Scale (AIS) of ASIA-A, ASIA-B, ASIA-C or ASIA-D as determined by a qualified examiner.
4. Autonomic dysreflexia can be present but is not a necessary requirement. This is defined as a rise of systolic pressure by more than 30 mm Hg during noxious skin stimulation or when the bladder or bowel is full, or apparently spontaneously over a period of minutes.
5. Pain (neuropathic) of moderate severity or greater is present, when the patient is taking medication, with a score of at least 4 on a numerical rating scale (range of 0 to 10).
6. Treatment with at least two of the following drug classes must have failed to give satisfactory pain relief within the last two years: anticonvulsants (e.g., pregabalin, gabapentin); antidepressants (e.g., trazodone, amitriptyline); NSAIDS (e.g., ibuprofen). In addition, at least one of the following must have proved ineffective: exercise-based rehabilitation, massage therapy using a variety of methods, acupuncture using pressure, needles, heat, or electrical stimulation on specific points on the body and psychological interventions such as cognitive therapy.
7. Participants on medications for other conditions, such as diabetes, will be considered as candidates for this study. The dose will be monitored throughout the trial. (They will be excluded if the drug is being used to treat epilepsy, Parkinson's diseases, or other brain degenerative diseases.)
8. The subject must be willing to comply with the protocol including all scheduled visits.
9. Literate at 8th grade level or above.
10. The subject must provide a letter of clearance for the DBS surgery from their primary physician.

Main Criteria for Exclusion

Major Exclusion Criteria: Admission to study.

Exclusion Criteria	Measure	Rationale
Unable to give informed consent	Clinical examination	Protection of human subjects
Prisoner or ward of the state	History	Vulnerable population
Pregnancy	Urine or serum pregnancy test	Risk to fetus
Prior history of abusing non-prescribed drugs	History	Vulnerable population
Recent (one-year) history of alcohol abuse	History	Vulnerable population
ASIA motor exam unobtainable	ASIA Motor Score	Baseline scoring needed for determination of change in score
History of cardiac arrhythmia	History and ECG tracing	Higher risks of arrhythmia with DBS
Renal disease, heart disease or uncontrolled hypertension, liver disease or hepatic cirrhosis	History	Highly variable rates of recovery
Active major medical or psychiatric illness (MMSE<25)	History	Vulnerable population
Significant post-traumatic encephalopathy from head trauma sustained at SCI	History	Vulnerable population
Languages without local expertise	Family history	Lack of personnel or appropriate outcomes scales
Pain is only nociceptive, due to muscle spasm	Physical examination	Neuropathic pain is therapeutic target

Major Exclusion Criteria: Treatment/Intervention procedure:

1. Coagulopathy requiring anticoagulation therapy
2. Thrombocytopenia or platelet dysfunction
3. Peripheral vascular disease
4. Comorbid neurological diseases or disorders, including a history of seizures
5. Active systemic infection or concurrent immunosuppressive therapy
6. Existing implantable cardiac pacemaker, defibrillator or neurostimulator
7. Requiring short-wave or microwave diathermy treatment during the course of the study.
8. Inability to cooperate
9. Any contraindication to MRI studies (All future MRIs, with the exception of brain MRIs, are excluded.)
10. Adverse reaction to stimulation (such as inability to stimulate at analgesic levels without causing clinical hypertension or hypotension) or allergy or hypersensitivity to any materials of the neurostimulation system
11. Depression, as defined by a Beck Depression Inventory (BDI-1a) score of 30 or above.
12. Subjects with any clinically significant abnormality, not expected on the basis of age (age-related), that is seen in magnetic resonance imaging (MRI).

Approximate Number of Patients	A maximum of 12 participants with incomplete or complete SCI and neuropathic pain at or below the level of injury.
Approximate Number of Study Centers	Two sites (VA Medical Center & University of Miami - Miller School of Medicine)
Concomitant Medication	Concomitant medications and treatments or procedures pertinent to the study treatment or to any adverse events will be recorded including: 1) name of drug, treatment, or description of procedure, 2) start and end dates and times, and 3) clinical indication and/or findings. Investigational drugs and any other intervention (not part of the guidelines for management of SCI) known to have a potential impact on outcome will be prohibited. Participants will be allowed to utilize over-the-counter drugs such as NSAIDs, acetaminophen and aspirin. Their use will be documented in the weekly pain assessments. A list of "allowed" medications will be provided to study participants. After the surgery, patients will be allowed to stay on the protocol if they take Tramadol (50-100 mg, 2 times a day for up to 2 weeks) as a rescue drug in addition to their stable medication. The patient must be taking pain medication to maintain a stable level of medication from 4 weeks before surgery to 12 weeks after (the primary endpoint), except on the day of surgery. On the day of the surgery, in the presence of a physician who can provide immediate backup pain control if needed, medications will be stopped until the acute effects of DBS on analgesia have been evaluated. On week 20 during a patient visit under medical supervision, patients will be instructed to take one fewer tablet or a smaller dose tablet, wait 4 hours and then see if their pain becomes worse. If it does become worse, they may take medication to reach the original dose. Subsequently, they may follow this procedure at home or during the following visits.

Study Intervention (Device Usage Protocol)	
Device	The study will use PMA authorized, Class III, implantable, Neurostimulation Systems for Deep Brain Stimulation. The Medtronic Activa PC and PC+S DBS device systems will be used as designed without any modifications.

Study Intervention (Device Usage Protocol)	
Device Implant Procedure	Participants presenting to the trial site with a history and mechanism consistent with chronic SCI with neuropathic pain below the level of injury, will be assessed using defined screening tests. Eligible participants will also undergo a multi-step consent process. Upon successful consent, trained and certified study personnel will perform imaging and neurological systems exams. The neurological systems exams will be utilized as the baseline measure of neurological status including neuropathic pain and autonomic dysreflexia. Upon successful completion of screening and baseline measurements, participants will undergo surgery to implant unilateral or bilateral DBS Leads (Model 3387S), extensions (Model # 37085 or 37086) and implantable neurostimulator (IFN) (Model 37601, or Model 37604). After successful implantation and one week recovery, subjects will participate for 44 weeks in the study.
Treatment group	Single treatment group. Ethical considerations forbid a control group that receives implant surgery without stimulation. Hence participants must serve as their own controls.
Frequency	One-time implantation of Activa PC or Activa PC+S Deep Brain Stimulation device system. Continuous stimulation, or cycled in 12-hour on/off periods, or in shorter on/off periods, for ~ 40 weeks. Voltage range 0.1-10V.
Safety Evaluation	1) Although preclinical data and clinical experience suggests DBS and device implantation is relatively safe, several adverse events are possible and will be noted, 2) Comprehensive pain, motor and autonomic assessment will occur on screening and enrollment (baseline) and then at every on-site visit week throughout the study. 3) The correct functioning of the DBS apparatus will be monitored at 4-week intervals after implantation until study week 24, and at 8-week intervals thereafter. 4) Pain Assessments using the ISCIPDS:B will evaluate development of neuropathic pain syndromes.
Secondary outcomes	1) Tilt table response exam 2) Autonomic Standards Assessment (BP, HR, sympathetic skin response)

Safety Analysis Plan	
Primary Safety Analysis	The analyses for safety will focus on changes in reported pain intensity during routine patient visits. All AEs and SAEs will be listed and their incidence compared to historical controls. The primary endpoint analyses will occur at 44 weeks post-implantation.
Secondary Outcomes and Analyses	The secondary hypothesis concerns autonomic assessment that will also take place during routine patient visits. Heart rate, blood pressure, sweating, body temperature and breathing will also be classified as normal, abnormal, unknown or not obtainable. Lower urinary tract, bowel and sexual function will also be scored. Comprehensive testing sessions will analyze vagal and sympathetic influences on the cardiovascular system, measuring blood pressure and heart rate variability (power spectrum analysis) during sit-up or tilt-table challenge. Assessment of motor and non-pain somatosensory function will be done during visits every 4 weeks. Clinical sensory testing will include Light Touch and Pin Prick tests defined in the ASIA standards [1]. The Beck Depression Inventory (BDI-1a) will also be used, to assess emotional function in neuropathic pain [4]. If BDI assessment (>30) suggests suicidal thoughts, the Columbia Suicide Severity Rating Scale will be used in consultation with a clinical psychologist.

4 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

1. Jonathan Jagid, MD, is an Associate Professor in the Department of Neurological Surgery University of Miami. He will serve as a Principal Investigator and have overall responsibility for the conduct of the study, including study and database design, data and statistical analysis, and publication of results.
2. Ian Hentall, PhD is an Associate Professor in the Departments of Neurological Surgery / Miami Project to Cure Paralysis, University of Miami. He will serve as a Co-investigator and share responsibility for clinical protocol compliance.
3. Corneliu C. Luca, MD, is an Assistant Professor of Neurology in the Department of Neurology, University of Miami. He will serve as a Co-investigator, share responsibility for clinical protocol compliance and adjust the stimulators during subject visits in accordance to the protocol timeline.
4. Alberto Martinez-Arizala, MD, is the Chief of the Spinal Cord Injury Service at the Miami VA Medical Center. He will serve as a Co-investigator, share responsibility for clinical protocol compliance and will be involved in patient screening, and performing evaluations of neurological status in all participants.
5. Gustavo Alameda, MD, is a Neurologist specialized in spinal cord injury at the Miami VA Medical Center. He will serve as Co-investigator, and share the responsibilities for clinical protocol compliance and clinical assessment of subjects with Dr. Martinez-Arizala at the MVAMC.
6. Eva Widerstrom-Noga, PhD, is a Research Professor in the Department of Neurological Surgery / Miami Project to Cure Paralysis, University of Miami. She will serve as a Co-investigator and, as an expert on the psychology and measurement of spinal cord injury pain; she will conduct and interpret comprehensive pain and other psychological assessment on patients.
7. James Adcock, ChE, MBS, is a Senior Research Associate at the Miami Project to Cure Paralysis. He will assist Dr. Widerstrom-Noga on pain measurement by presenting stimuli and capturing data.
8. Letitia Fisher, is a Clinical Research Coordinator in the Department of Neurosurgery / Miami Project to Cure Paralysis, University of Miami. She will serve as Study Coordinator and will be responsible for regulatory compliance, ethical approvals, data collection and entry in the study case report forms, monitoring study staff for protocol compliance, scheduling and conducting visits with participants.
9. Diana D. Cardenas, MD, MHA, is Professor and Chair of the Department of Rehabilitation Medicine, University of Miami and Chief of Service & Medical Director, Rehabilitation Medicine Hospital, Jackson Memorial Hospital. She will serve as Medical Monitor and will perform the following duties: assess all participants for significant potential adverse events throughout the trial, determine if an adverse event requires reporting to the Principal Investigator, Sponsor, IRB, and FDA, and report findings and recommendations to the Principal Investigator.
10. M. Ross Bullock, MD, PhD, is Clinical Director of the Neurotrauma Program at The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine. He will serve as Medical Monitor and will perform the following duties: assess all participants for significant potential adverse events throughout the trial, determine if an adverse event requires reporting to the Principal Investigator, Sponsor, IRB, and FDA, and report findings and recommendations to the Principal Investigator.

5 LIST OF ABBREVIATIONS

Abbreviation	Term
AEs	Adverse Events
AIS	ASIA Impairment Scale
ASIA	American Spinal Injury Association
BPI	Brief Pain Inventory
CNS	Central Nervous System
CRFs	Case Report Forms
CT Scan	Computerized Axial Tomography
DBS	Deep Brain Stimulation
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practices
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
INS	Implantable Neurostimulator
ISCI	International Spinal Cord Injury
ISNCSI	International Standards for Neurological Classification of Spinal Cord Injury
LANNS	Leeds assessment of neuropathic symptoms and signs (Pain scale drawings)
LFP	Local field potential
LUT	Lower Urinary Tract
MPCP	Miami Project to Cure Paralysis
MPI	Multidimensional Pain Inventory
MRI	Magnetic Resonance Imaging
MVAMC	Miami Veterans Administration Medical Center
NRS	Numerical rating scale (0-10)
PI	Principal Investigator
QLI	Quality of Life Index
QoL	Quality of Life assessments
SAEs	Serious Adverse Events
SCI	Spinal Cord Injury

Abbreviation	Term
SCIM III	Spinal Cord Independence Measure
TBD	To be Determined
TEAE	Treatment Emergent Adverse Event
UM HSRO	University of Miami Human Subject Research Office
UMH	University of Miami Hospital
UMMSM	University of Miami Miller School of Medicine

6 DEFINITION OF TERMS

	Term	Definition
6.1	**Adverse Experience (AE)**	The term "adverse event," as used by the Sponsor, is synonymous with the term "adverse experience," which is used by the FDA. An adverse event is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with a Sponsor study drug, regardless of causal relationship. This includes but is not limited to the following: • Any clinically significant worsening of a preexisting condition. • Any recurrence of a preexisting condition. • An AE occurring from overdose of a Sponsor study drug whether accidental or intentional (e.g., a dose higher than that prescribed by a health care professional for clinical reasons). • An AE occurring from abuse of a Sponsor study drug (e.g., use for nonclinical reasons). • An AE that has been associated with the discontinuation of the use of a Sponsor study drug.
6.2	**Clinical Trial/Study**	Any investigation in human patients intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product or device, and/or to identify any adverse reactions to an investigational product or device, and/or to study absorption, distribution, metabolism and excretion of an investigational product with the object of ascertaining its safety and/or efficacy.
6.3	**Co-investigator**	An individual member of the clinical trial team (e.g. MD, DO, PA) designated and supervised by the Principal Investigator at a trial site to perform critical trial-related medical procedures and/or to make important trial-related decisions.
6.4	**Good Clinical Practice (GCP)**	A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reportable results are credible and accurate, and that the rights, integrity and confidentiality of trial patients are protected.

	Term	Definition
6.5	**Informed Consent**	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
6.6	**Institutional Review Board (IRB) or Independent Ethics Committee (IEC)**	An independent body of medical professionals and non-medical members, whose responsibility it is to ensure the rights, safety and wellbeing of patients involved in a trial. This is accomplished by, among other things, reviewing, approving and providing continuing review of trial protocol and amendments and of the methods and materials to be used in obtaining and documenting informed consent of the trial patients.
6.7	**Investigator Brochure**	A written document that contains a detailed and current review of all relevant clinical trials. It includes when applicable, chemical and pharmaceutical data, toxicological, pharmacokinetic, and pharmacodynamic data in animals, and the results of earlier clinical trials.
6.8	**Monitoring**	The act of overseeing the process of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), GCP and the applicable regulatory requirements.
6.9	**Patient**	A person who receives medical care.
6.10	**Principal Investigator**	The person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the Investigator recorded in box 1 of the Form FDA 1572 is the responsible leader of the team and may be called the Principal Investigator. (See Subinvestigator)
6.11	**Quality Assurance (QA)**	All those planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded), and reported in compliance with applicable regulatory requirements.
6.12	**Regulation**	Regulation refers to all applicable regulations, laws, and guidelines. This study will be conducted according to all applicable regulations. The regulations include but are not limited to the Code of Federal Regulations (United States); Good Clinical Practice; the International Conference on Harmonization (ICH) and the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Patients.

	Term	Definition
6.13	**Regulatory Agency**	Regulatory Agency refers to all appropriate health and regulatory agencies. These may be local, national, or international and include, but is not limited to, the US Food and Drug Administration (FDA).
6.14	**SAE (Serious Adverse Event)**	Any adverse drug/device experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
6.15	**Serious Adverse Event (SAE) Report**	A special form completed by the Investigator and forwarded to COMPASS for reporting all serious adverse experiences (regardless of cause) and for any death (regardless of cause) that occurs while on study or within 30 days of study completion.
6.16	**Sponsor**	Sponsor refers to Sponsor and representatives such as contract research organizations that are being used for the study.
6.17	**Statement of Investigator (Form FDA 1572)**	A form that represents a contract between a clinical Investigator and the FDA. This contract represents the investigators' commitment to conduct the clinical trial in accordance to all the regulations and laws that govern the conduct of clinical trials.
6.18	**Study Device**	Any drug, device or biological agent (including placebo) required by the protocol and supplied by the Sponsor for use in the Sponsor's clinical research and development studies.
6.19	**Study Start Date**	Date on which first patient signs informed consent form.
6.20	**Subinvestigator**	(See Co-investigator)
6.21	**Unexpected Adverse Experience**	Any adverse experience, the specificity or severity of which is not consistent with the current Investigator’s Brochure.

7 INTRODUCTION / BACKGROUND

7.1 Target Disease

Chronic spinal cord injury (SCI) entails loss or abnormality of autonomic regulation, motor control and body sensation at and below the dermatomal level of injury. When disconnection is incomplete, some degree of below-injury function remains. About one half of all new cases in the US are incomplete [5]. In principle, surviving functional connections are a hopeful sign, offering a target for possible therapies, as well as giving the patient some possibility of control distal to the lesion. In practice, unfortunately, these connections often entail dysfunction. For example, persistent pain below or at the injury level is experienced in 2/3rd of chronic SCI patients. As a result of this pain at least 1/3rd of this sub-population faces a severely reduced quality of life [6]; some authorities consider this rate to be much higher, based on surveyed pain ratings [7]. It was reported that 23% of a sample patients with cervical or high thoracic SCI and 37% with low thoracic or lumbosacral SCI would sacrifice sexual, bowel and bladder function for good pain relief [8].

SCI pain is typically a mixture of nociceptive pain, which is caused by activation of primary afferents' receptors, and neuropathic pain, which is caused by damage to the nervous system. The neuropathic pain of SCI is most frequently treated by anticonvulsant agents. There is good evidence from randomized control trials for some degree of effectiveness of gabapentin [9-11] and pregabalin [12,13], with weaker evidence for valproic acid [14]. Tricyclic antidepressants are also used to control SCI pain, but the supporting evidence is not as strong. Thus amitriptyline has proved somewhat effective when the patient is depressed [15,16], but trazodone was reported not to reduce post-SCI neuropathic pain more than placebo [17]. Traditional analgesics are also useful. Morphine can provide effective relief of neuropathic pain due to SCI, and can be combined with the alpha-2 agonist clonidine for this purpose [18,19]. Subarachnoid or epidural lidocaine has been used to obtain short-term relief [20]. For the musculoskeletal pain in SCI, which nociceptive, antispasticity agents are frequently used; intrathecal baclofen, for example, can be fairly effective [21,22]. Despite this considerable range of choices, pharmacological treatment for the pain of SCI remains inadequate. Low effectiveness, tolerance, side effects or difficulties with prolonged local administration (e.g., subdural) are among problems encountered [23].

Autonomic functioning after SCI depends on the injury level. Visceral efferents are damaged directly by mid-thoracic or sacral injuries. Higher control of autonomic function is degraded after cervical or high thoracic SCI, when only vagal control remains. Autonomic dysreflexia (AD) is a frequent consequence of cervical or high thoracic injuries. It mostly occurs when the lesion is above the 6th thoracic segment. Its estimated frequency is 48-90% in patients with tetraplegia or high quadriplegia [24-26]. AD is a cluster of symptoms caused by a massive sympathetic outflow, which includes elevated blood pressure, headache, flushing, sweating above the lesion level and abnormal heart rhythms. It is typically provoked by activity in visceral or cutaneous afferents below the injury. Distension of bladder or colon, such as occurs from loss of control of evacuation, may precipitate AD. It can occur sporadically, triggered several times each day, but sometimes it lasts for many days, since the patient is generally unaware of aggravating stimuli below the injury level.

Various categories of antihypertensive agents are used for symptomatic control of AD, in particular nitrates (e.g., topical nitroglycerin), calcium blockers (e.g., nifedipine) and selective alpha-adrenergic antagonists (e.g., prazosin, terazosin) [27]. In the short-term, these treatments are generally adequate. However, because AD can present as an acute crisis, long-term treatment with an effective blocking dose is poorly matched to the breakthrough of symptoms and their chronic sequelae. Alpha-adrenergics, for example, in addition to their adverse acute effects and contraindications, produce receptor upregulation with long-term use. Additional problems are specific to SCI. Norepinephrine facilitates movement generation in the spinal cord and is a transmitter at sphincter muscles of hollow organs. Blockade of its principal alpha-1 receptors can therefore exacerbate functional deficits in SCI.

Deep brain stimulation (DBS) is increasingly being used instead of drugs (or in combination with them) for several neurological problems. Its most common application at present is to control the symptoms of advanced Parkinson's disease and essential tremor by stimulation in the basal ganglia or sub-thalamic nucleus [28,29], which has been provided to well over one hundred thousand patients worldwide. Patients can greatly reduce or eliminate their intake of L-dopa or other drugs (anticholinergics, dopamine antagonists, etc.). DBS, because it is targeted to a particular brain region, considerably reduces the possibility of adverse neural and systemic effects compared to most pharmacological approaches. Since the choice of DBS targets has a good basis in scientific investigation, the treatment is not merely empirical. Another key advantage is that the dose can be instantaneously modulated in various ways (e.g., voltage, pulse width, pulse frequency), including immediate stopping. Initial high cost seems to be the main disadvantage. Discounted over the predicted lifespan of the average patient, however, costs may compare favorably with drugs, especially if the lower probability of adverse effects is taken into account.

Extensive experience with DBS in motor disorder patients has led to various technical improvements. Failures due to equipment breakdown, infection or improper targeting, for example, are becoming rare. This success has led to consideration of DBS for other chronic neurologic maladies, such as obsessive-compulsive disorder, depression and epilepsy [30]. It has also prompted a reconsideration of DBS as a treatment for chronic, drug-refractory pain of various sorts, which was used for many years prior to the advent of DBS for motor disorders [31]. DBS for pain control can target several different brain regions. One main target is the midbrain periaqueductal gray (PAG) together with the nearby periventricular gray (PVG); another is the sensory thalamus (ST). Reported long-term pain alleviation rates have been higher with PAG/PVG stimulation (79%) than with ST stimulation (58%) [31]. Cortical sites are also sometimes targeted for pain (Nguyen et al.), but these have apparently not worked well for SCI pain [32] and are not considered further here.

7.2 Conduct and Monitoring of Study:

This study will be conducted in compliance with the protocol, and monitored according to Good Clinical Practices as outlined in 21 CFR 312 Subpart D and E6 ICH: Good Clinical Practice Guidance and other applicable regulatory requirements.

7.3 Overview of Target Patient Population:

Veterans or non-veterans will be recruited, for a total of 12 participants. They will be men or women, fluent in English, of average literacy, 22-60 years of age, with an incomplete or complete SCI and neuropathic pain at or below the level of injury. We anticipate few or no females, because females are about 20% of the general injured population in the US [5] and because females are under 20% in most military branches and were fewer in previous years. The data obtained from this study may provide additional data to warrant extension of similar, future studies to additional populations.

8 LITERATURE REVIEW

8.1 Animal Studies

Traumatic spinal cord and brain injury are prime examples of neurological syndromes in which the key to permanently enhanced recovery lies in accentuating beneficial trophic effects. The present proposal stems in part from the preclinical studies of Dr. Ian Hentall, one of the co-investigators. These animal studies were based on the hypothesis that brainstem raphe nuclei function to promote repair [33]. Raphe nuclei release serotonin nearly ubiquitously in brain and spinal cord. Serotonin is a neurotrophic molecule as a well as a classical neurotransmitter [34]. Along with 5-HT, many raphe neurons co-release peptides with neurotrophic effects, e.g., thyrotropin releasing hormone, galanin [35,36]. Some raphe neurons are known to be excited by diverse sensory and chemical correlates of trauma, e.g., pain, hypotension, circulating cytokines [37], suggesting a restorative feedback loop. This model can be extended to midbrain raphe nuclei

with ascending divergent projections. After experimental fluid-percussion brain injury, it was found that one week of stimulation in the median or dorsal raphe nucleus boosted behavioral recovery (forelimb reaching, water-maze learning) and anatomical recovery (forebrain white matter, hippocampal neuron density) [33]. Molecular mechanisms for these effects are currently under investigation. For example, spinal cord concentrations of the key restorative molecule cyclic adenosine monophosphate (cAMP), which are greatly reduced by SCI, were returned to normal by 2 hours of NRM stimulation given 3 days post-injury, as were various downstream protein signaling targets of cAMP (unpublished).

The earlier SCI work of this laboratory focused on acute thoracic (T8) injuries, testing both the PAG and the nucleus raphe magnus (NRM), which is the PAG's main hindbrain relay to the spinal cord. Several days of stimulation in either region partially restored motor performance and normalized mechanical allodynia in forelimbs [38,39]. In histological analysis, myelination of white matter around the injury zone was seen to have recovered significantly when either site was stimulated. The NRM also significantly increased serotonin-containing terminals in gray matter.

In recent unpublished studies with PAG stimulation, PAG stimulation was tested in rats with an acute cervical (C5) injury. One week of intermittent stimulation yielded long-term improvement in AD 7 weeks later, as measured by mean carotid pressure during colon distension (Figure 1).

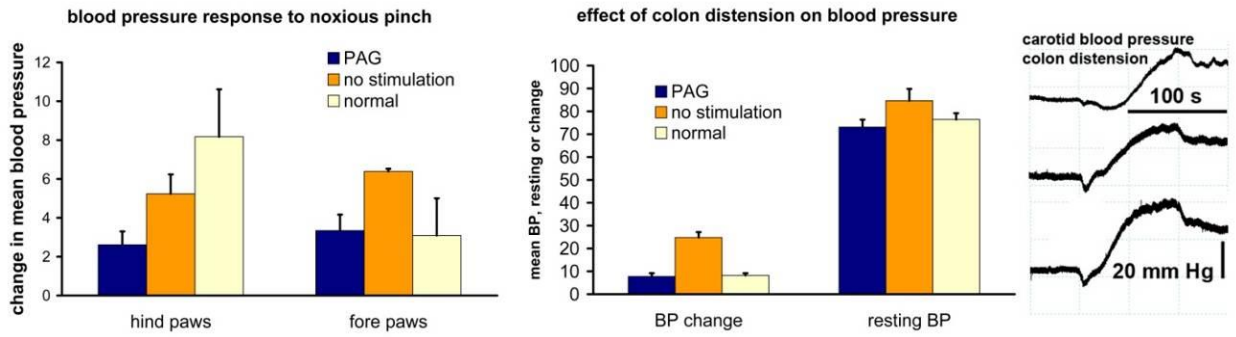

Figure 1. Cervical (C5) contusional incomplete SCI was made by a controlled force impactor in rats. The PAG was stimulated for 1 week, starting 2 hours after SCI, applied for 12 hours daily through a tungsten microelectrode. Stimulus trains were 30 µA, 1 ms, 8 Hz cathodal pulses, given in 5-minute periods alternated with 5 minutes of rest. A carotid artery cannula measured blood pressure responses during colon distension (3 cc, with a balloon catheter) or pinching of a hindpaw or forepaw. Autonomic dysreflexia evoked by colon distension 7 weeks after the SCI was clearly lower after the PAG stimulation. Data points for colon distension are averages of 3 trials of pressure applied for 100 s at 10-minute intervals, as illustrated by the traces on the right. Blood pressure changes during noxious pinch were reduced by PAG stimulation. However, hind paw responses were higher in normal rats than in injured rats, suggesting a complex interaction between sensory and autonomic recovery.

In additional studies with PAG stimulation, 3 weeks of stimulation applied 6 weeks after C5 contusion improved recovery in motor tests of grip strength and angle of postural stability on an inclined plane (Figure 2). More weeks of stimulation appear to be needed for older injuries.

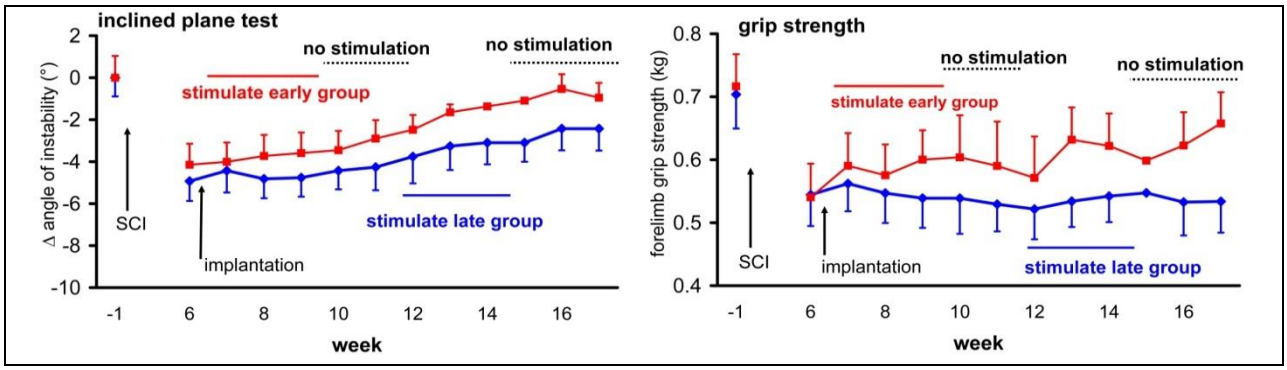

Figure 2. PAG stimulation, with parameters as in Figure 1, was applied for 3 weeks, starting either 7 weeks ("early") or 12 weeks ("late") after C5 contusional SCI. Significant differences occurred in repeated measures analysis between the two interventions in the inclined plane test (left) and grip strength (right).

Both the chronic and the acute treatments in these studies had the histochemical effect of reducing immunostaining to calcitonin-gene related peptide (CGRP) near the injury. Since CGRP is a key pain transmitter in the spinal cord, and is increased by SCI [40], this potentially important pain-reducing mechanism.

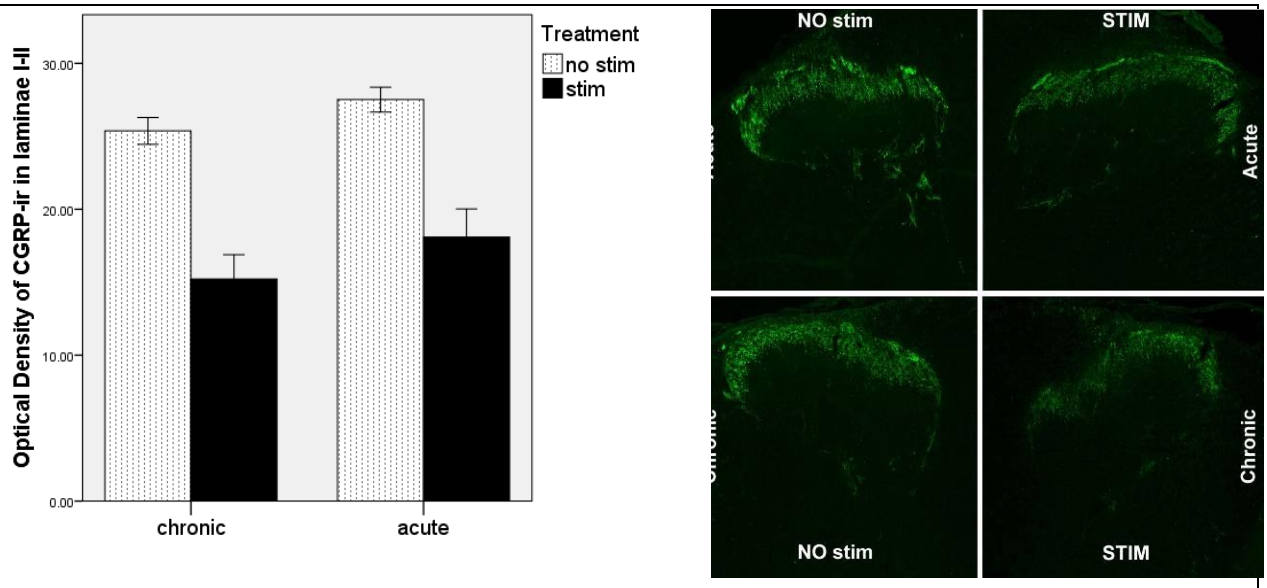

Figure 3. Staining for CGRP 1 cm caudal to a C5 SCI in rats treated with PAG stimulation after acute or chronic SCI.

Other recent work has focused on breathing. The C5 moderate contusion in rats was treated with 3 weeks of NRM stimulation with standard parameters as above. Breathing was monitored by whole body plethysmography in unrestrained rats. Minute volume was improved both during and after treatment weeks (Figure 4).

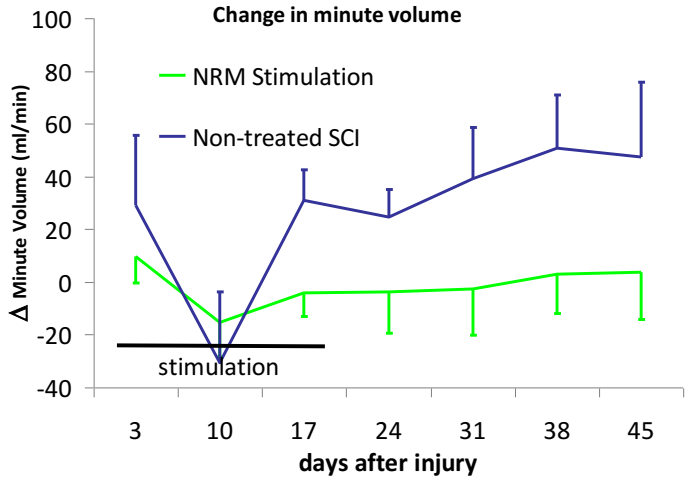

Figure 4. The minute volume after C5 injury. All data has been normalized from baseline. There were significant differences between treatment groups (both n=6, p=.017, SPSS v19 repeated measures ANOVA).

Conclusion

DBS in the midbrain PAG/PVG reverses ongoing pain in man. However, the data are too few to judge safety or efficacy for SCI pain. Because current drug or cognitive therapies fail to control SCI pain in a significant proportion of cases, a renewed assessment of DBS in the PAG/PVG is justified. The assessment should involve a detailed characterization of pathology, treatment and outcome. Pain alleviation could also reduce ongoing autonomic dysreflexia [41], while preclinical findings suggest that permanent partial improvements in pain, autonomic deficits and motor performance could occur after prolonged stimulation. In man, spontaneous partial recovery has been noted many months after SCI, perhaps due to patterned neural activity [42]. DBS in the PAG/PVG could accentuate this restorative activity.

Comparative advantages expected of DBS for treating SCI are as follows:

- Permanently improve symptoms, not merely relieve them.
- Every type of deficit recovers, not just, for example, limb movement or sensation
- No untoward effects of prolonged stimulation, based on by animal research
- Dose can be immediately reduced or discontinued if adverse effects appear
- Existing technology can be translated without modification to the treatment of SCI
- Trophic DBS has a strong scientific support basis and theoretical basis in repair models
- Can readily be combined in a non-interfering way with drug or cell implant therapy

8.2 Efficacy and Safety Data for DBS in Humans

The total numbers of patients that have received DBS for any type of pain is relatively small, around a few hundred have been reported. Only a small fraction of these had SCI pain. Based on two reviews, confirmed by a Medline search, we have created the following inclusive list of published primary reports of DBS for SCI pain. One review contains a meta-analysis of all published studies of DBS for pain that met adequate criteria for patient selection, pain evaluation and follow-up duration, which included cases of SCI pain. The other review focuses on DBS for SCI pain [32]. Details on the age and injury level, the method of pain assessment and basic surgical details, such as the stimulation site, are sometimes unclear or absent, especially in the earlier reports

Technical neurosurgical terms in DBS. (1) “Internalization” is the technical neurosurgical term for completing the acute implantation surgery by leaving the electrode in the brain and connecting it to a subcutaneously implanted electronic controller. (2) This controller is also referred to as a “generator”. (3) “Leads” is another name for electrodes.

1. 12 SCI patients, 5 internalized [43]. Two leads were implanted, one in PVG and one in ST, specifically in the ventral posterior lateral nucleus of thalamus (VPL). Cases were classified as Brown-Sequard (n=1), myelopathy (n=2), tetraplegia (n=1), post-dorsal root entry zone lesion (n=1), paraplegia (n=5), conus syndrome (n=1); syringomyelia (n=1); plexus avulsion (n=1). Patients were studied for 7 days before internalization of electronics and connector cables, which proceeded when a 50% or more pain reduction on a visual analog pain scale was achieved by a voltage that was 50% of the threshold for aversive responses. Reported aversive responses were paresthesias from ST stimulation and floating, and dizzy or warm feelings from the PVG. Five patients met the criterion for internalization of electronic stimulators and connecting cables. Long-term pain relief was seen in the following cases, all n=1; percentages shown are relief relative to pre-operative pain levels: myelopathy (25-50%), tetraplegia (0-25%), post-DREZ lesion (75-100%), plexus avulsion (0-25%), paraplegia, (0-25%). Most patients received stimulation at both sites; the plexus avulsion case received only PVG stimulation.

2. 4 SCI patients, 3 internalized [44]. Pain in individual patients was distributed: in both lower extremities below T10, in all extremities below C5, in both lower extremities below T9, in the right lower limb (n=1). The first three cases were implanted bilaterally in the ventrocaudalis thalamic nucleus; the fourth received one lead in ventrocaudalis and one in the PAG/PVG. The first, third and fourth patients were internalized and experienced benefits lasting from 2 months to 5 years.
3. 3 SCI patients, 1 internalized [45]. All sites were ST. "One case of lower limb pain after excision of a neurofibroma of the lumbar region and two cases of gunshot wounds causing partial paraplegia." They "…experienced two early failures and one late failure because of tolerance development during the course of 2 years".
4. 8 SCI cases, 3 internalized [46]. There were 2 long-term successes, characterized as "almost complete pain relief" and "the patient's ability to resume a normal pain-free life". All sites appear to have been in ST (VPL).
5. SCI patients, 3 or 4 internalized [47]. The authors summarize their results as follows. "Fourteen electrodes, 7 sensory thalamic and 7 PAG/PVG, were implanted in 11 patients with pain secondary to spinal cord injury. Two of each class of electrodes were internalized (36%). No patient obtained long term pain relief with DBS".
6. 6 SCI patients, 5 internalized [48]. One patient had excellent relief and two had partial relief. Injuries are not described. Sites were ST (VPL) with or without PVG or PAG stimulation.

This choice of sites reflected the view that ST should be targeted for neuropathic pain and PAG/PVG for nociceptive pain, since SCI pain is typically a mixture of nociceptive and neuropathic pain [49]. However, the neuropathic pain of SCI is mechanistically distinct from other central neuropathic pains (e.g. post-stroke or thalamic pain syndrome) [50].

Insertion of electrodes in the PAG/PVG is reported to cause short-term analgesia [44]. Yet insertion could quite likely produce the opposite effect in some participants, temporarily blocking the stimulation-produced analgesia, which would have been excluded by the selection criteria typically used, leading to underestimates of potential success rate.

In summary, the total number of reported cases involving DBS surgery for SCI pain was 44. Only 21 were internalized, that is, involved applying DBS beyond the neurosurgical operation. The majority of SCI pain cases were given stimulation in either the ST or the ST combined with the PAG/PVG. There are 3-4 cases of PAG/PVG stimulation without concomitant ST stimulation. Some of these were not typical spinal cord trauma. Thus existing data are too few to assess whether or not PAG/PVG stimulation is effective against SCI pain. Changes in other SCI symptoms were not described. A beneficial effect on autonomic dysreflexia is possible, since PAG/PVG stimulation inhibits the types of nociceptive pain that elicit it.

9 STUDY DEVICE

9.1 Device Description

The Activa PC Deep Brain System as shown in Figure 1 below consists of the neurostimulator, leads, extensions, and clinician and patient programmers. The Activa PC primary cell neurostimulator (model 37601) is a multi-programmable device that can deliver electrical stimulation through one or two leads implanted in the brain. Stimulation is provided by controlled delivery of current from a battery in an implantable neurostimulator (INS) to metal leads (electrodes) surgically implanted in the brain. The INS is typically placed in the pectoral location or near the collarbone. Current is conducted to the electrodes via electrical conduits, including extensions (Models 37085 and 37086) and leads (model 3387), which are tunneled subdermally through the neck, travel through the skull, and terminate in a neural structure appropriate to the neurological disease being treated. The Activa PC system is capable of providing stimulation to 2 leads, each with 4 electrode contacts. Stimulation parameters are adjusted to optimize therapy for the patient. They can be independently controlled and include the following: active electrode(s), electrode polarity, pulse width, amplitude, and frequency. The stimulation settings are stored in programs. A program is a specific combination of pulse width, rate, and amplitude settings acting on a specific electrode combination on a lead, or on a lead and the INS, in unipolar mode. Up to four programs can be combined into a group. Pulse width, amplitude, and electrode polarity are independently programmed for each program within a group. Rate, rate limits and cycling for each program within a group must have the same values. Stimulation is delivered to a maximum of two implanted leads (one lead per hemisphere), with a maximum of 4 electrodes per lead. Rate is limited to 250 Hz, pulse width is limited to 450 µsec, amplitude is limited to 10.5 V (or 25.5 mA) and the charge density warning threshold is 30 $\mu C/cm^2$/phase.

Stimulation programs are controlled by the clinician via the N'Vision Clinician Programmer. A patient programmer (model 37642) will enable the patient to deactivate the device and can output an event log.

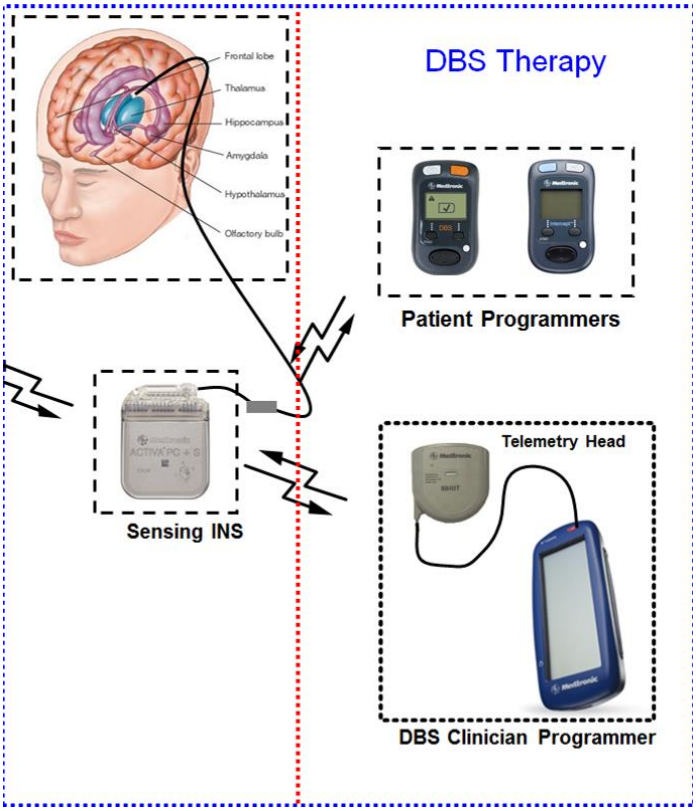

Figure 5: Activa PC System

The Activa PC+S DBS Implantable System will have therapy equivalent to Activa PC. This equivalence includes stimulation capabilities (pulse width, rate amplitude, modes) and the use of the same model 8840 Clinician Programmer and software, model 37642 patient programmer, and leads as the Activa PC system. In addition, sensing capability is included in the Activa PC+S implantable neurostimulator (INS), which is the same from factor as Activa PC. Sensing is controlled and its data managed with a User-intuitive research interface, a Clinician Sensing Programmer. This tablet programmer interfaces to the INS via telemetry and to a personal computer via USB. The Clinician Sensing Programmer will not adjust or control therapy. Likewise, the 8840 Clinician Programmer and the two Patient Programmer models will not adjust or control Sensing. In addition, the Medtronic Activa PC+S 8180 Sensing Software will be used. Medtronic Activa PC+S 8180 Sensing Software is part of a neurostimulation system for deep brain stimulation used to exclusively program the Medtronic Activa PC+S Model 37604 Implantable Neurostimulator for sensing of brain electric field potential. The Activa PC+S Sensing Software system components consist of: the Activa PC+S 8180 Sensing Software, the 8181 Sensing Tablet, and the SMTP (Sensing Programmer Telemetry Module). The Medtronic Activa PC+S 8180 Sensing Software, along with the Sensing Tablet and the SPTM, uses telemetry, a radio-frequency (RF) communication, to configure, record, and retrieve sensing information obtained from the Medtronic Activa PC+S 37604 Implantable Neurostimulator.

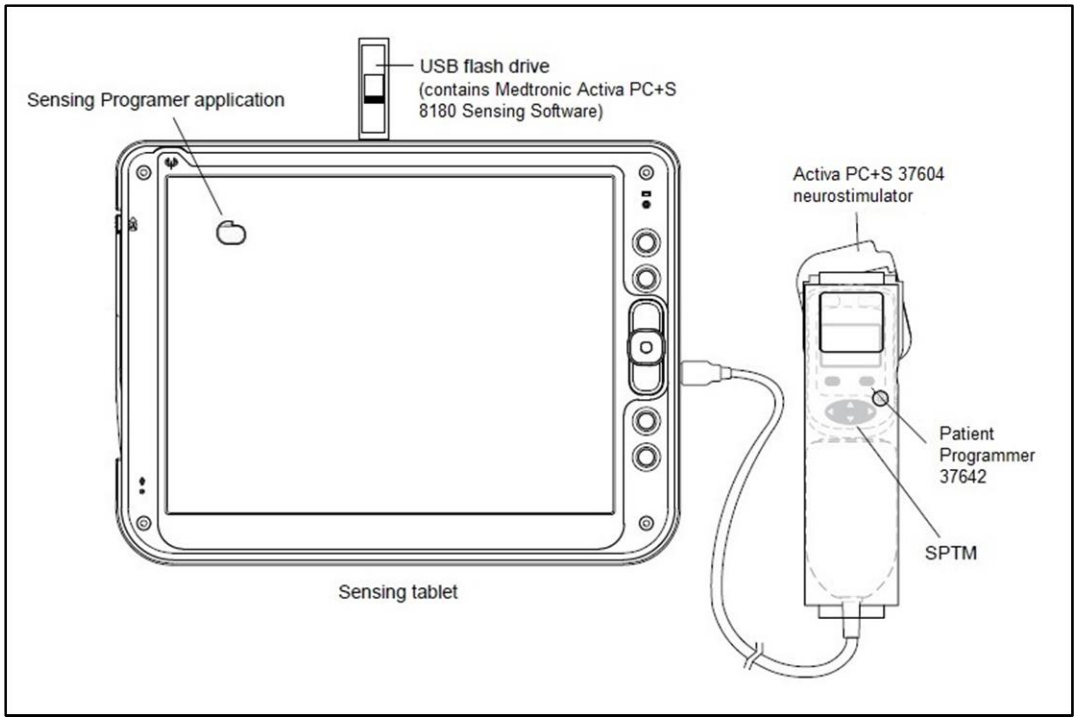

Figure 6. Activa PC+S Sensing Software System

10 RISK ANALYSIS

The rationale for unilateral or bilateral DBS implants is based on the potential benefits that may be produced. For participants with chronic SCI, the benefits anticipated from DBS include reduction or alleviation of neuropathic pain. A beneficial effect on autonomic dysreflexia is also possible, since PAG/PVG stimulation inhibits the types of nociceptive pain that elicit it.

The risks of the device implant surgery (to the participants) in this study are identical and no more than those associated with current DBS surgery for Parkinson's treatment. The risks include, but are not limited to, bleeding, transfusion, infection, sensory impairment, paralysis, speech arrest, stroke, seizure, intracerebral hemorrhage, coma, and/or death. The participants will be made aware of the risks in writing and in person. These participants will all be consented prior to entering the study.

To minimize surgical risks, exposure to general anesthetic, and additional stereotactic frame placement in one cranial procedure (as opposed to two separate) will be used to implant bilateral devices. This approach falls under the standard of care for DBS neurosurgery.

There is potential throughout the study of adverse events occurring related to the implant itself. These include but are not limited to, erosion of the device through the skin, migration or movement of the hardware in the brain, delayed infection of the device, battery failure, and/or mechanical failure of the device. These complications may necessitate further surgery to correct. However, it is important to note that the safety profile of this device and the surgical procedure is well established, and investigator(s) are well trained and have previously conducted several hundred identical implant procedures.

10.1 Risk minimization

The study protocol contains several measures to minimize risk, many adopted based on the experience in standard DBS surgery (Parkinson's trial or other experiences that are relevant to the risk minimization measures that will be used). These include the design that the therapy is completely reversible (it can be fully explanted without damaging neuronal or muscular tissue). The user also has the ability to instantaneously turn off the device with the Patient Controller. Additionally, participants will have 24 hour access for contacting study personnel.

If subjects have an implanted programmable pump, such as an intrathecal baclofen (ITB) pump, risk will be minimized as follows. The neurostimulator (generator) will be placed at least 8 inches from the pump and/or on the opposite side of the body. Whenever the pump or neurostimulator is reprogrammed, each device will be checked before the patient leaves a programming session to ensure that the other device was not inadvertently affected. Patients will be told to contact their physician immediately if they experience symptoms (such as spasms) that could be related to either device or to the medical condition treated by either device. Subjects with implantable pump systems will be evaluated for MR compatibility (susceptibility to magnetic fields) prior to MR imaging.

11 STUDY OBJECTIVES AND PURPOSE

11.1 Purpose/Objective

We propose an investigation of the safety of deep brain stimulation (DBS) for the alleviation of chronic neuropathic pain in patients with spinal cord injury (SCI). The stimulation will be applied bilaterally or unilaterally in the midbrain periaqueductal-periventricular gray region (PAG/PVG). Indications of efficacy will also be examined. Patients will receive bilateral implants in the case of complete SCI (ASIA-A). Patients with an incomplete SCI who can localize pain to one side of the body will receive unilateral stimulation of the PAG contralateral to the sites of pain.

Although PAG/PVG stimulation has been used previously in SCI pain patients, the small numbers of patients studied and the lack of detail on their testing and injury status makes a phase I trial appropriate. Effective treatment of pain could also bring benefits to patients with autonomic dysreflexia (AD), which can be provoked by painful visceral and somatic stimuli below an incomplete lesion. Autonomic functioning will therefore be studied as a secondary outcome. Preclinical evidence from rats suggests that prolonged PAG stimulation may lead to enduring improvements in all deficits (sensory, motor, and autonomic). The proposed study will therefore examine if such improvements occur when PAG/PVG stimulation is applied over many weeks.

Aim 1 is to determine whether DBS in the PAG/PVG at analgesic intensities produces any systemic or neurological adverse effects in patients with longstanding SCI (>1 year), either immediately or as a result of prolonged application for up 40 weeks.

Aim 2 is to determine whether acute application of DBS in the PAG/PVG influences the severity of spontaneous ongoing pain caused by longstanding SCI.

Aim 3 is to determine whether DBS in the PAG/PVG affects stimulus-evoked or persistent hypertension (a major sign of autonomic dysreflexia) in chronic SCI patients.

Aim 4 is to determine whether prolonged PAG/PVG stimulation (for 10 months) leads to cumulative changes in chronic pain severity, motor or autonomic symptoms in chronic SCI patients.

11.2 Core (null) Hypothesis:

The null hypothesis is that, in humans, deep brain stimulation (DBS) applied bilaterally or unilaterally in the midbrain periaqueductal-periventricular gray region (PAG/PVG) will not alleviate chronic neuropathic pain in patients with spinal cord injury (SCI).

11.3 Primary Objectives:

To evaluate the safety and efficacy of deep brain stimulation (DBS) applied bilaterally or unilaterally in the midbrain periaqueductal-periventricular gray region (PAG/PVG) for alleviation of chronic neuropathic pain in patients with spinal cord injury (SCI).

11.4 Secondary Objectives:

To assess the clinical effects of DBS on autonomic functioning when PAG/PVG stimulation is applied over many weeks (44 weeks); to determine with Activa PC+S whether local field portentials in the PAG/PVG can be used to predict the efficacy of DBS in this region.

12 STUDY DESIGN

12.1 Type of Study

Phase 1, open label study.

12.2 Expected Number of Participants

Twelve (12) participants with SCI for >1 year and show chronic persistent pain that has not fully responded to drug treatment.

12.3 Treatment Groups

One (1) Treatment group. All participants will receive the same treatment (long-term DBS in PAG/PVG) and undergo the same procedural protocol. Ethical considerations forbid a control group that receives implant surgery without stimulation. Hence participants must serve as their own controls.

After internalization of the pulse generator (electronic stimulator) and subcutaneous tunneling of connecting cables to the electrode and 12-48 hours for recovery from this internalization procedure, stimulation will be applied to the patient. The patient will be asked to report their ongoing pain level, on a 0-10 numerical rating scale (NRS) with the stimulation turned off and, for each electrode contact, in small voltage steps up to the threshold for any aversive effects (if not seen in the first step). Floating, dizzy or warm feelings can be expected, based on literature reports. If there is no ongoing pain, cutaneous brushing to cause allodynia below the injury, at sensitive sites determined in the pre-surgical testing sessions, will be used. Blood pressure will also be measured by cuff before and during electrical stimulation. This will be repeated on week 12 The optimal level will be 67% of threshold for aversive or other unwanted effects (e.g. motor) or device maximum (10 V) if such effects are not observed. We expect the optimal voltage to be 4-10V. A frequency range of 10-20 Hz and pulse width range of 250-450 μs is anticipated, but these parameters will be set according to the subject's responses. The subject returns home with the optimal stimulation settings after each programming session.

Subjects will receive monthly adjustment of stimulation levels to optimize analgesia on the NRS. They will be given the option of remaining in the study if any level becomes unpleasant in later months.

The subject will be given up to 4 different program groups after study week 16, differing in contacts, voltages, frequencies and pulse widths, all determined to be without adverse effect by the clinician programmer in the in-person office session. The subject is asked to switch program groups using their patient programmer. They switch immediately if relief is unsatisfactory, and stay with the best program for pain relief, or with any adequate program if the best is not determined, keeping a pain diary (score 0-10) at intervals of 24 hours or less to help determine the best program group.

If the subject reports effects of DBS on sleep, the stimulation will be cycled in appropriate 12-hour on and off periods in a 4 week trial period and maintained if superior. Also, if the subject does not tolerate continuous stimulation for many hours, cycling at shorter intervals (e.g., one-hour on and off periods) will be tested.

Although all subjects receive the same DBS treatment, a subset will receive the PC+S device for additional sensing of brain signals. After regulatory permissions have been obtained, the next subject to reach surgical consent (stage 3 consent) will receive this device. Subsequent enrollees will also receive the Activa PC+S DBS system.

12.4 Schematic diagram ("Study Flow Charts") of trial design, and procedures

A. Table 1 lists the major procedures relevant to this study.

B. Table 2 contains the flow sheet which shows the frequency and timing of all visits.

12.5 Description of the Measures Taken to Minimize/Avoid Bias

As this is an open label safety study without a control group, no specific measures will be taken (e.g., randomization, blinding, etc.) to minimize /avoid bias. Subjects will not be randomized, and all will receive the same pattern. The subject and the primary evaluator will not be blinded to the stimulation level. Long-term changes over the course of the treatment will be analyzed by time-series analysis of the adjusted stimulation levels. Placebo effects from surgery, as well as the safety and stability of the DBS implant, will be analyzed when the stimulator is inactivated during programming adjustment sessions by investigators.

12.6 Duration of Subject Participation

- Participants will be monitored throughout a one year evaluation period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, neurological status.

- Safety and efficacy assessments will be performed at week 1 and 2 post-intervention and at 4-week intervals post-intervention from study week 8 until study week 24, and at 8-week intervals thereafter until study week 48 . The last one of these assessments will take place on study week 52. The week 52 assessment will include a qualitative exit interview with audio recording. The subject and investigators will be given the opportunity for open comments and questions concerning elements of the study.

- After the initial 52-week study period subjects can choose to remain in the study for an extended period lasting approximately 104 weeks. The details of this extension period are covered next in section 12.6.1.

12.6.1 Extension of study

Introduction. The study will be extended for approximately 2 more years, precisely 104 weeks. The purpose is to obtain long-term follow-up information on safety and efficacy, in subjects that have opted to receive continuing brain stimulation. We label weeks in terms of original enrollment. Thus the surgery occurs in weeks 7 and 8 and the original study finishes in week 52, with the extension lasting from week 53 to week 156.

Aims:

1. To evaluate any changes in pain relief in the 2nd and 3rd year of deep brain stimulation (DBS) in the midbrain periaqueductal/periventricular gray (PAG/PVG).
2. To assess needs for changes in stimulation parameters (contact selection, voltage, frequency, pulse width) to continue optimal relief.
3. To determine changes in injury status revealed by the ASIA score.
4. To uncover later-occurring adverse effects.

Enrollment. Subjects will preferably continue without a gap at the end of the original 52 week study. However, they may be enrolled at any time during the extension to accommodate the time needed to obtain regulatory approval for the extension or subjects who wish to take a break. An additional informed consent form will be used for enrollment.

Procedures. Subjects will receive continuous DBS in the PAG/PVG from the previously implanted system. They will return every 12 weeks to the study site to optimize the stimulation parameters for pain control. The optimum may drift or may not have been determined previously from the very large range of possible settings. Subjects will leave the visits with a blinded choice of settings (2 to 4, labeled A, B, C D), which they can explore at home. Preliminary findings suggest that pain changes over several days when settings are changed, and that slow recursive testing is the best way to find the optimum. Subjects may request visits

at other times for stimulation adjustment or other study related issues. Some later subjects may have a PC+S generator device implanted, which allows recording from the stimulating leads. Subjects with this device will also undergo brief recording sessions during visits, following the protocol of the first year.

Tests and questionnaires. The study extension will use only questionnaires and study forms from the original study. It will omit autonomic system testing and quantitative sensory testing. On-site assessment will be done in clinical exam rooms and offices of the Miami Project to Cure Paralysis of the University of Miami Miller School of Medicine, including ASIA assessment. If the stimulator settings are producing consistent adequate pain relief, visits may be omitted at the subject's discretion, except for weeks 104 and 156, and assessments will be made by telephone questionnaire.

The following will be assessed every 12 weeks.

International Spinal Cord Injury pain basic data set (ISCI)
Neuropathic Pain Symptom Inventory (NPSI)
Beck depression inventory (BDI)
Guy-Farrar patient global impression of change (PGIC)
Medication usage

In addition, subjects will be asked to keep a pain diary with a morning and evening pain score rated from 0 (no pain) to 10 (worst ever pain). The pain diary will be retrieved at the visits or by telephone.

At weeks 104 and 156, we will determine the ASIA score (American Spinal Injury Association neurological examination, sensory and motor). On week 156, an open ended qualitative exit interview will be conducted with audiovisual recording, including questions on the overall experience, effects on daily life, etc.
Adverse events (AEs) will be recorded immediately after telephone contact by the subject (subject-reported AEs) and during visits to the study site (clinician-reported AEs).

- **Table 1: List of Procedures for planned study**

	Screening:	
1	Urine pregnancy test	
2	HIV, HBV, HCV testing	
3	Laboratory tests (CBC, CMP, BSCP, prothrombin time test)	
4	Medical history, Brief neurological and medical examination	
5	Autonomic dysreflexia assessment	
6	Spinal Cord Injury history	
7	ASIA motor / sensory scores	
8	Functional and pain assessments	
9	Psychological Assessment (MMSE, BDI)	
10	Drug abuse screening test	
	Baseline Procedures (at 2- weeks):	
1	Autonomic dysreflexia assessment	
2	Functional and pain assessments	
3	Psychological Assessment (MMSE, BDI)	
4	ASIA motor / sensory scores	
5	Medical history, Brief neurological and medical examination	
6	Patient diary on medications	
	DBS Device Implantation Surgical Procedure:	
1	Initial MRI / CT scan of the spine	
2	Chest X-ray; Electro-cardiogram	
3	1-Targeting & Lead placement: at 7-week	
3	2-DBS & Lead connection: at 8-week	
	ICU Monitoring/Medical Treatment:	
1	Blood Pressure Monitoring	
2	Oxygenation	
3	Additional physiological monitoring specific to subject (displayed on telemetry monitor)	
4	Laboratory tests (CBC, CMP, BSCP, prothrombin time test)	
5	Post op medications (antibiotics, DVT prophylaxis, etc.)	
	Follow-Up Procedures:	
1	Long-term DBS in PAG/PVG starting on week 8	
2	Telephone interview: weekly, except on-site visit weeks, from week 3	
3	Pain assessments: on even weeks, starting on week 10	
4	Autonomic Standards Assessments: on on-site visit weeks	
5	Tilt table response exam: at 20-week, 32-week, and 52-week	
6	Beck Depression Inventory: on visit weeks	
7	Folstein Mini-Mental State exam: at 20-week, 32-week, and 52-week	
8	Patient Global Impression of Change: weekly, starting on week 9	
9	ASIA motor and sensory assessments: at 20-week, 32-week and 52-week.	
10	Qualitative exit interview at 52 weeks	

Table 2. Flow sheet of Visits/Assessments

Study Visit Schedule for the initial 52-week study period:

week (±7 days) >>	<<No of tests	1	2	3, 5	4, 6	5,6	7	8	9, 11, 13, 15, 17, 19	10, 14, 18	12, 16	20, 32	21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51	22, 26, 28, 30, 34, 36, 38, 42, 44, 46, 50	24, 40, 48	52
SCREENING		x														
SURGERY, or week-5,6 screening for surgery						x	x	x								
LONG-TERM DBS in PAG/PVG (note 1)									x	x	x	x	x	x	x	x
TAPERING or STOPPING of PAIN MEDICATION(S)												x			x	
COMPREHENSIVE TESTING	4		x									x				x
ABBREVIATED TESTING	5										x				x	
TELEPHONIC INTERVIEW	40			x	x				x	x			x	x		
Sites																
Miami VA Medical Center (note 2)		x	x								x	x			x	x
Miami Project in Lois Pope Life Center (note 2)				x	x				x	x	x	x	x	x	x	x
University of Miami Hospital						x	x	x								
Study Therapy																
Targeting and lead placement	1						x									
DBS and lead connection	1							x								
DBS adjustment &-or sensing / possible 5 minute inactivation	9							x			x	x			x	x
General Assessments																
Informed Consent	3	#1	#2			#3										
Spinal Cord Injury history/Demographics	1	x														
Medical history, Brief medical examination	1	x														
Drug Abuse Screening Test (DAST)	1	x														
Folstein Mini-Mental State Examination (MMSE)	4	x										x				x
Beck Depression Inventory (BDI)	9	x									x	x			x	x
(PGIC)	44								x	x	x	x	x	x	x	x
Adverse Event assessment	52		x				x	x	x	x	x	x	x	x	x	x
Vital signs (BP, SpO2, temp)	12	x	x				x	x			x	x			x	x
Patient Diary on Medications	50	x	x	x	x				x	x	x	x	x	x	x	x
Qualitative exit interview	1															x
Neuro System Exams																
ASIA Neurological Exam	4	x										x				x
Tilt table response exam (note 3)	4		x									x				x
Patient Self-assessment of Autonomic Responses	38			x	x				x	x			x	x		
Autonomic Standards Assessment	9		x								x	x			x	x
Multidimensional Pain Inventory (MPI-SCI)	4		x									x				x
Quantitative sensory testing (QST)/Allodynia	4		x									x				x
ISCI Pain Basic Data Set / NPSI	25		x		x					x	x	x		x	x	x
Imaging																
Neuroimaging - MRI study	1					x										
Neuroimaging - CT study	1						x									
Electro-cardiogram (EKG)	1					x										
Chest x-ray	1					x										
Laboratory																
CBC, Comprehensive Metabolic Panel (including Mg++, Renal & Liver Function), PT/PTT	2	x				x										
Urine Pregnancy (note 4)	2	x				x										
HIV, Hep B, Hep C serology	1	x														

1 All General Assessments and Neurological System Exams, i.e., BDI, MMSE, QST, Pain (ISCI PBDS, NPSI, MPI-SCI), PGIC, during this period will occur prior to DBS adjustments.

2 Pain testing may take place at either site

3 Not required if determined subject can't tolerate it to completion

4 Urine pregnancy test for premenopausal women

12.7 Description of the "Stopping Rules" or "Discontinuation Criteria" for Individual Participants, Parts of Trial, and Entire Trial.

A. Termination by the Participants

Participants may withdraw consent to participate in this study at any time by informing the Principal Investigator. No further procedures will be performed or information will be collected from participants that withdraw consent. Previously collected data and samples will be used for the study analysis.

B. Termination by the Sponsor

The Sponsor may terminate the study at any time for any of the following reasons:

- Failure to enroll patients.
- Protocol violations.
- Inaccurate or incomplete data.
- Unsafe or unethical practices.
- Questionable safety of the study device.
- Administrative decision.

C. Termination by the Principal Investigator:

The Principal Investigator may remove a subject from the study at any time for any of the following reasons (Note: If the PI removes a subject prematurely, the PI shall promptly provide the IRB/IEC and the Sponsor with a written statement describing why the study subject was removed prematurely).

- Onset of confounding neurological problems such as severe dysesthesia, severe neuropathic pain, or changing neurological level.
- Serious adverse event: discontinuation due to a serious adverse event.
- Lost to follow-up: the subject fails to return to the study site for scheduled visits and does not respond to attempts to contact.
- Withdrew consent: the subject decides to stop his participation for any other reason than an adverse event, or is unable to complete the study as described in the study protocol.
- Administrative: the Sponsor decides to terminate an individual subject or decides to discontinue the study due to general safety concerns.
- Protocol violation: anything that is a direct and significant violation of the clinical study protocol.

D. Partial Termination

If the treatment appears at any point to be clearly successful in any patient, the choice of constant stimulation at the best amplitude will be offered. Regardless of whether the stimulation is stopped permanently or left at a constant level, the patient will be followed according to the study plan for as long as they remain willing. The patient may also elect to receive no further stimulation but to stay in the full study to assess pain and other variables.

E. Futility and Enrichment:

Gradual benefits may be seen from prolonged treatment. Therefore the study will not be stopped early in the absence of interim benefits, nor will the stimulation intensity be increased.

13 SELECTION OF PARTICIPANTS

13.1 Recruitment Procedure

Some recruitment will be done through the newsletter of the Paralyzed Veterans of America (South Florida Chapter). This is a congressionally chartered Veterans service organization, whose members are veterans of the armed forces who have experienced SCI. In addition, participants will be solicited through the newsletter of the Miami VAMC. Other potential subjects will be identified from a database maintained by The Miami Project to Cure Paralysis. Potential study participants will be asked to contact Dr. Martinez-Arizala, Chief of the Spinal Cord Injury Service of the Miami VA Medical Center, if they are interested in learning more about the study. Dr. Martinez-Arizala will also conduct a medical record review to identify potential participants among the patients who in the past or currently are visiting his clinic. These patients will be contacted by Ms. Fisher (Study Coordinator) who will inform them about the study over the phone or by sending them a copy of the recruitment material in the mail.

Compensation will be provided for each visit (n=10), as a fixed amount ($100.00 per visit) to cover expected average travel and incidental costs. An extra payment will be given for participation in the entire study ($400.00). If a patient does not have a telephone, an inexpensive pay-as-you go cellular telephone will be provided (from additional internal funding sources).

13.2 Consent Procedures

Informed consent will be obtained in 3 steps: (1) for clinical and psychological screening, (2) for the main functional testing, (3) for DBS surgery. The Study Coordinator and Dr. Martinez-Arizala will address questions during steps 1 and 2 (to be done in the 1st week at the Miami VA Hospital). This will be done in a private examination room, with the patient offered the possibility of reviewing the informed consent form and asking questions for up to 2 weeks before deciding (they would need to make a 2nd visit for this); Drs. Jagid and Luca will be present for step 3 (to be done in the 7th week at the University of Miami Hospital). The step 2 consent process will include showing the patient the surgical (step 3) consent form, and explaining the surgery, in order for the potential participants to have 6 weeks to review the surgery consent and ask any question they might have about the procedure. The step 3 consent will explain that the subject may receive the Activa PC+S DBS device system or the Activa PC.

Participants will be screened before the step 2 consent discussion for drug abuse or major psychiatric problems. Literacy is an inclusion criterion. Participants can request a meeting or telephone conversation at any time during the study with the PI or relevant Co-investigator, as well as with the Study Coordinator. The Study Coordinator will be the primary contact for this. Her email address and telephone numbers will be provided to participants for this purpose.

A pregnancy screen will be performed on all females of potential child bearing age. All SCI patients excluded following the screening will be recorded to identify potential factors impeding patient enrollment which can be addressed by the study Executive Committee. Patients unable to provide informed consent will be denied entry into the study. The fully executed informed consents will be placed in the chart, with copies given to the patient and maintained in the site's study binder.

13.3 Inclusion Criteria

a) Age: 22 - 60 years old at last birthday;

b) Diagnosis of traumatic SCI at or above the 12^{th} thoracic segment (T12) that occurred >365 days;

c) Neuropathic pain below the level of injury, as determined based on pain in an area with neurological deficit and described as burning, shooting, electric, stinging etc.

d) The injury must have occurred at least 1 year prior to entering the study and participants must have experienced chronic pain for a minimum of six months.

e) The disability must have a grade on the American Spinal Injury Association Impairment Scale (AIS) of ASIA-A, ASIA-B, ASIA-C or ASIA-D as determined by qualified examiners.

f) Pain (neuropathic) of moderate severity or greater is present, when the patient is taking their routine pain medication, with a score of at least 4 on a numerical rating scale (range of 0 to 10).

g) Participants who are on medications for other conditions, such as diabetes, will be considered as candidates for this study. The dose will be monitored throughout the trial. (They will be excluded if the drug is being used to treat epilepsy, Parkinson's diseases, or other brain degenerative diseases.)

h) Participants will be allowed to utilize over-the-counter drugs such as NSAIDs, acetaminophen and aspirin. Their use will be documented in the weekly pain assessments. A list of "allowed" medications will be provided to study participants. After the surgery, patients will be allowed to take stay on the protocol if they take Tramadol (50-100 mg, 2 times a day for up to 2 weeks) as a rescue drug in addition to their stable medication.

i) The patient must be taking pain medication to maintain a stable level of medication from 4 weeks before surgery to 12 weeks after (the primary endpoint), except on the day of surgery. On the day of the surgery, in the presence of a physician who can provide immediate backup pain control if needed, medications will be stopped until the acute effects of DBS on analgesia have been evaluated.

j) The participant must be willing to comply with the protocol including all scheduled visits.

k) Autonomic dysreflexia can be present but is not a necessary requirement. Autonomic dysreflexia will be defined as rise of systolic pressure by more than 30 mm Hg during noxious skin stimulation or when the bladder or bowel are full, or apparently spontaneously over a period of minutes

l) Literate at 8th grade level or above.

m) Treatment with at least two of the following drug classes must have failed to give satisfactory pain relief within the last two years: anticonvulsants (e.g., pregabalin, gabapentin); antidepressants (e.g., trazodone, amitriptyline); NSAIDS (e.g., ibuprofen). In addition, at least one of the following must have proved ineffective: exercise-based rehabilitation, massage therapy using a variety of methods, acupuncture using pressure, needles, heat, or electrical stimulation on specific points on the body and psychological interventions such as cognitive therapy.

n) The subject must provide a letter of clearance for the DBS surgery from their primary physician.

13.4 Exclusion Criteria

a) Any failure to meet above criteria;

b) Pregnant women or women who are contemplating pregnancy.

c) Prior history of abusing non-prescribed drugs.

d) A recent (one-year) history of alcohol abuse.

e) Renal disease, heart disease or uncontrolled hypertension, liver disease or hepatic cirrhosis.

f) Active major medical or psychiatric illness; a score of less than 25 on the MMSE.

g) Significant post-traumatic encephalopathy from head trauma sustained at SCI.

h) Pain is only nociceptive, due to muscle spasm

Additional Surgical Exclusion Criteria:

1) Coagulopathy
2) Thrombocytopenia or platelet dysfunction
3) Inability to cooperate
4) Any clinically significant abnormality, not expected on the basis of age (age-related), that is seen in magnetic resonance imaging (MRI).
5) Peripheral vascular disease.
6) Depression, as defined by a Beck Depression Inventory (BDI-1a), score 30 or above.
7) Existing implantable cardiac pacemaker, defibrillator or neurostimulator.
8) Diathermy treatment during the course of the study (unless limited to brain and cervical spine and using a head send-receive coil
9) Adverse reaction to stimulation (such as inability to stimulate at analgesic levels without causing clinical hypertension or hypotension) or allergy or hypersensitivity to any materials of the neurostimulation system
10) Comorbid neurological diseases or disorders, including a history of seizures

13.5 Withdrawal Criteria:

a) Participants may withdraw consent to participate in this study at any time by informing the Principal Investigator. No further procedures will be performed or information will be collected from participants that withdraw consent. Previously collected data and samples will be used for the study analysis;

b) The only anticipated circumstance under which the Principal Investigator would terminate a subject's participation is if information was obtained which made the subject ineligible for the study. The primary reason for this premature termination is to be indicated by selecting one of the following definitions:

- Gradual deterioration in neurological status from incomplete to complete SCI, or change in ASIA grade to a more severe level: B to A, C to A or B, D to A or B or C;
- Unresolved post-surgical wound infection;
- Onset of confounding neurological problems such as severe dysesthesia, severe neuropathic pain or changing neurological level;
- Serious adverse event: discontinuation due to a serious adverse event;
- Lost to follow-up: the subject fails to return to the study site for scheduled visits and does not respond to attempts to contact;
- Withdrew consent: the subject decides to stop his participation for any other reason than an adverse event, or is unable to complete the study as described in the study protocol;
- Administrative: the Sponsor decides to terminate an individual subject or decides to discontinue the study due to general safety concerns;
- Protocol violation: anything that is a direct and significant violation of the clinical study protocol.

14 TREATMENT OF PARTICIPANTS

14.1 Recruitment and Screening Procedures and Assessments:

Screening and recruitment of participants will take place at the Veterans Hospital and at The Miami Project to Cure Paralysis. Participants will be inpatients or outpatients at Veterans Hospital or University of Miami Hospital (UMH). After admission, the PI or designated representative will be informed of the patient and their history will be carefully screened for relevant selection criteria (as outlined in Table 1, and Table 2 in section 13.6) and the patient's MRI of the spine will be reviewed. Patients with spinal cord transection and contusive signal change exceeding 3 cm in length will not be eligible for the study. Eligible patients will be informed of the study, counseled regarding its key steps, and procedures, and asked to provide Informed Consent.

14.2 Method of Assigning Participants to Treatment Groups:

Not applicable. This study will employ an open label, non-randomized, and non-placebo controlled design. There will be only one treatment group.

14.3 Participant Procedures and Assessments

14.3.1 Baseline Assessments

Participants who remain eligible after all the screening procedures are complete will undergo the following baseline assessments at 2- week, prior to surgical procedures.

- Functional Pain Assessments
    - ISCI basic pain dataset and Neuropathic Pain Symptom Inventory (NPSI)
    - West Haven-Yale Multidimensional Pain Inventory for persons with SCI (MPI-SCI)
    - Allodynia testing
    - Quantitative sensory testing (QST)
- Quality of Life assessments
    - Beck Depression Inventory (BDI, version 1a)
- Autonomic Assessment:
    - Autonomic Standards Assessment (BP, HR, sympathetic skin response)
    - Tilt table exam response.

14.3.2 Surgical Procedures and Assessments.

The surgical procedure for implantation of a PAG/PVG deep brain stimulator is described here. The procedure technique is no different than FDA approved deep brain stimulator procedures for movement disorder. All patients undergo MRI imaging of the brain prior to surgery. Particular imaging sequences consist of thin cut (1-2mm) T1 and T2 weighted images. On the morning of surgery, in the pre-anesthesia holding area, a Cosbid, Robert, Wells (CRW) frame is rigidly affixed to the skull with four point fixation. This is done with local anesthetic injections consisting of .5% Marcaine with epinephrine 1:200,000, a total of 20-30cc is usually used.

Once the frame is in place, the patient will undergo a CT scan of the brain without contrast agent. This CT scan has the localizer rods in place, which create a stereotactic field for precise localization of target. The imaging studies including the CT scan and the prior obtained MRI are uploaded into a Medtronic planning station which allows for manipulation of the images and targeting of the periaqueductal gray. The computer

then outputs an X, Y, and Z coordinate for the chosen target. More than one MRI scan may be necessary if determined by the neurosurgeon, in order to obtain optimal image resolution and fusing with the CT scan by the planning station software.

The patient is then placed on the operating room table in the supine position with the head elevated approximately 45°. The patients head is fixed in this position with the use of the frame. The entire head is then shaved and the right frontal area of the scalp approximately 11cm back from the nasion and 3.5cm off the midline on the right side is injected with approximately 20cc of 0.5% Marcaine with 1:200,000 epinephrine. The CRW arc with the X,Y, and Z coordinate for the target is then applied to the CRW frame. A small curvilinear incision is then made and a 14mm burr hole is made using a Midas Rex drill. A burr hole cap is applied to the circumference of the burr hole. The dura is then opened using electrocautery exposing the underlying cortical surface. An 11-blade scalpel is then used to score the pia. At this point, a Ben-Gunn Stage is applied to the CRW arc and a cannula is inserted down the center channel of the Ben-Gunn through the burr hole, traversing the right frontal lobe to end at a depth of 25mm above the desired target.

With the use of neurophysiologic monitoring the target is optimized for lead placement. Neurophysiologic monitoring for this target, the periaqueductal grey, is not well defined. Therefore, targeting will be primarily based on image guidance. The lead (model # 3387) itself is then inserted to a pre-defined depth of 237mm. This will place the tip at the chosen target.

Test stimulation will be performed to determine the adequacy of targeting. The patient will report feelings evoked by various stimulation parameters to be sure that appropriate stimulatory effects are felt and that no adverse stimulatory effects are induced at normal programming thresholds (see 14.7).

After confirmation of target accuracy the lead is secured in place. A lead protector is placed over the distal end of the lead which is tunneled into a subgaleal pocket over the right parietal boss. The frontal scalp incision is closed with a combination of 2-0 vicryl and staples. The CRW frame is then removed from the patients head. An additional CT scan may be performed after the lead implantation procedure to confirm target and ensure no trauma has occurred.

General anesthesia is induced, and the patient is endotracheally intubated. The operating room table is turned 90° and the patients head turned 70° to the left, placed on a donut head holder with a roll under the shoulder blades to put the neck in slight extension.

The surgical sites are then prepped and draped sterilely. Local anesthetic is injected using 0.5% Marcaine with 1:200,000 epinephrine. A three finger-breadth linear incision is made two finger-breadths below the right clavicle and a subcutaneous pocket is made just over the pectoralis fascia. A counter-incision is made over the distal lead at the parietal boss and the lead is exposed at the parietal boss. The distal lead protector is removed. A subcutaneous passer is used to make a subcutaneous tract from the parietal boss counter-incision to the subclavicular incision. An extension cable is tunneled down the passer and brought out of the subclavicular incision. The passer is then withdrawn and the proximal portion of the extension is connected to the distal portion of the lead. The distal portion of the extension is connected to the superficial channel of the neurostimulator. The neurostimulator and excess extension cable are then inserted into the chest wall pocket and anchored to the pectoralis fascia using a 3-0 prolene stitch. In subjects with implantable programmable pumps, the neurostimulator must be placed at least 8 inches from the implanted pump. The chest incision is re-approximated using 3-0 vicryl stitch in an interrupted, inverted subcuticular manner. Steri-strips are applied to the skin. The parietal boss incision is re-approximated by using 2-0 vicryl for the galea and staples for the skin.

14.3.3 Targeting & Lead Placement

Targeting is accomplished by combining high resolution 3T MRI images with thin cut CT scan images and the use of computerized targeting software. Images are uploaded into the targeting software. The computer then fuses both MRI and CT scans together. The operator of the computer is then able to identify certain

landmarks including the anterior commissure (AC) and posterior commissure (PC). The intercommisural length is then calculated. The actual target is then identified by using offsets from these structures. In the case of the periaqueductal grey, the X coordinate is 10mm posterior to the mid-commisural point, the Y coordinate is 2-3mm lateral to the wall of the IIIrd ventricle, and the Z coordinate is in the plane of the intercommisural line. T2 weighted images can then be used to further refine the target based on direct visualization of the periaqueductal grey.

Once the final target is identified, the computer yields an X,Y,Z coordinate for the stereotactic field. This is set on the CRW arc and used to deliver the lead.

14.3.4 Macrostimulation and Sensing

Once the lead is at target, test stimulation will begin with an external neurostimulator (model # 37022). Macrostimulation will be performed by a Neurologist who specializes in neurophysiologic monitoring for deep brain stimulation. He has been involved in well over 700 similar procedures. The macrostimulation procedure involves an algorithm that tests all combinations of contacts in a bipolar fashion. Both pulse-width and frequency will be set at fixed values and amplitude will be gradually increased in steps while recording clinical effects. The goal will be to determine optimal settings for therapeutic effects as well as suboptimal settings that induce side effects. It should be noted that all effects from stimulation are fully reversible by cessation of stimulation or revision of programming parameters. Upon successful intraoperative macrostimulation, the implantable neurostimulator (model 37601) will be connected.

Therapeutic effect can be elicited by the patient reporting a warm feeling in various areas of the body. No such feeling, however, does not preclude optimal targeting. Chronic stimulation may be needed to induce a beneficial effect.

Likewise, changes in vital signs will also be assessed as these changes are indicative of autonomic effects. Examples would be change in heart rate, systolic blood pressure, etc.

Neurologic changes would also be assessed as the periaqueductal grey is close to the superior colliculus and thus various eye findings might be induced.

If the subject reports effects of DBS on sleep, the stimulation will be cycled in appropriate 12-hour on and off periods in a 4 week trial period and maintained if superior. Also, if the subject does not tolerate continuous stimulation for many hours, cycling at faster on and off periods will be tested.

In subjects with an implanted PC+S device, the visits at weeks 12, 16, 20, 24, 32, 40, 48 and 52 will include recording of local field potentials. Recording will be done from all contacts during DBS at optimal setting for pain relief, over a period of one minute.

14.3.5 Monitoring Participant for Comfort

All participants will be arousable during surgery and thus able to vocalize any discomfort. Our institution has a specially trained anesthesia team adept at deep brain stimulation surgery and its particular nuances as it pertains to awake procedures. Patients will all be on a Precedex drip for sedation with intermittent dosing of remifentanyl for comfort.

The second surgery for generator internalization involves general anesthesia, skin incision and subcutaneous manipulation. Due to these factors (superficial post-operative pain, incomplete recovery from anesthesia), the subject may not be in a satisfactory state to be discharged on the surgery day, especially if scheduling factors cause a late surgery. Physician judgement will be used to decide whether an additional 1-2 days of in-hospital observation is appropriate.

Subjects or investigator-clinicians can request and carry out an additional unscheduled in-person visit to study sites at any time. This will be done if the subject has any perceived safety issues, or requests a change in stimulation parameters to improve pain control.

14.4 Lead and or DBS Removal

These devices have been designed and tested, with FDA approval for certain disorders, to be permanent implants. However, there are occasions in which the device or a portion of the system might need to be removed. If necessary, this requires additional surgery with risk.

The most common reason for removal is infection. At our institution, deep brain stimulation carries a 1.5% risk of infection necessitating removal. The majority of the time, the implantable neurostimulator and extension cables need to be removed with preservation of the intracranial lead. This is a result of the fact that most infections start at the neurostimulator implant site.

Alternative reasons for removal of the system would be patient request in the event that the device does not produce its intended results. However, in this instance, it is rare for patients to request removal as it requires additional surgery and there is no significant risk to keeping the device. Devices may also malfunction or break necessitating removal or revision surgery to fix.

Generators have a lifespan which ends at the time of battery failure. On average generator batteries fail after 3-5 years depending on stimulation parameters. Battery longevity depends also on sensing features. Thus it is expected that the battery of the Activa PC+S 37604 Neurostimulator will last less than that of the Activa PC 37601 (which does not allow for sensing). When considering the stimulation parameters currently being used in the study, the Medtronic reference manual for battery longevity of the Activa PC+S neurostimulation system for DBS estimates the longevity at roughly over 4.5 years. This number only represents an estimate, considering battery longevity depends on several factors: programmed parameters, system impedance, hours per day of stimulation, degree of patient control over programmable stimulation parameters, and the use of sensing features (in the case of the Activa PC+S system). This figure is based on stimulation frequencies >100 Hz as used in movement disorders; it is expected that pain treatment will use lower frequencies (<25 Hz) which will give at least 1-2 years more lifetime according to calculations based on manufacturer's confidential data (M949908A001, System eligibility and battery longevity manual for Activa PC+S). In the event that battery replacement would be needed, routine, same day, surgery is performed to remove and replace the generator.

14.5 Post Implantation Procedures & Follow-up

Procedures performed to evaluate the safety of the investigational procedures and to evaluate subject outcome for this study include:

A. Beginning one week after surgery, participants will undergo follow-up assessments post-implantation:

   i. Pain assessments every 2 weeks (ISCI basic pain data set, NPSI,), starting on week 10, will assess for development of, or changes in neuropathic pain; more comprehensive pain testing (MPI quantitative sensory testing/allodynia) will take place on comprehensive testing visit weeks (20-week, 32-week, and 52-week).

   ii. Autonomic Standards Assessment: on on-site visit weeks (BP, HR, sympathetic skin response) and on week 20, week 32, and week 52 (Tilt table response exam). Patient Self-assessment of Autonomic Responses occurs weekly starting on week 3, except on on-site visit weeks.

   iii. QoL assessments: on on-site visit weeks, starting on week 12 (Beck Depression Inventory (BDI-1a)) and weekly, starting on week 9 (Guy/Farrar Patient Global Impression of Change (PGIC));

   iv. ASIA motor and sensory assessments: on weeks 20, 32 and 52 to assess any improvement or deterioration in neurological function;

   v. a qualitative exit interview with audio recording at 52 weeks, giving subject and investigators will be given the opportunity for open comments and questions concerning elements of the study.

B. Follow-up assessments will take place either at the Miami VA Hospital or at The Miami Project to Cure Paralysis, Department of Neurological Surgery, for regular follow-up visits for 44 weeks post-surgery. At each visit, information will be collected regarding the safety of the treatment, the presence or absence of adverse side effects, and the efficacy of the therapy with respect to recovery of neurological functioning or the development of adverse effects.

14.6 Medication(s)/Treatment(s) Permitted (Concomitant Medications) and not Permitted Before and/or During the Trial:

A. Permitted Treatment

All medication taken by the participant during the study is to be recorded. All medications required to treat the participant should be administered as recommended. The following data will be recorded for all included participants up to the end of the study period: name of drug or nature of treatment, start and end dates, hours of administration, and indication. Fluid and blood replacement will be measured and documented on a daily basis. Additionally, any therapeutic or surgical procedure performed during the study period should be recorded, including the date, description of the procedure, and clinical findings

B. Prohibited Treatment

Investigational drugs and any other intervention (not part of the guidelines for management of SCI) known to have a potential impact on outcome are prohibited.

14.7 Procedures for Monitoring Participant Compliance

(Please Refer to Section 20 QUALITY CONTROL and QUALITY ASSURANCE)

15 SAFETY

Participants will be continuously monitored throughout a one (1) year evaluation period. Assessments will be performed as outlined in Table 1 and Table 2 in section 13.6. Assessments will also include monitoring of occurrence of AEs (acute, delayed, and/or cumulative), as well for changes in clinical status, neurological status and/or functional status. Safety will be determined as follows:

a) Adverse events or other safety concerns will be ascribed to one of two categories: (1) general known problems with all types of DBS (e.g. infection) or with untreated SCI (e.g., bladder control failure); (2) problems caused by the PAG/PVG site in particular (e.g., hypotension) or to a specific response of SCI symptoms to DBS (e.g., more pain). The first category will not lead to ejection of the method. The second category can be evaluated more by turning off the stimulation or examining correlations with the 4-week periods of (8-weeks after week 24) adjustment of stimulation amplitudes. Second-category events will be carefully assessed and will lead to discontinuation of the study treatment if they cannot be ascribed to special circumstances in a given patient.

b) Comprehensive pain, motor and autonomic assessment will occur on screening and enrollment (baseline) and then on on-site visit weeks (weeks 12, 16, 20, 24, 32, 40, 48 and 52).

c) The correct functioning of the DBS apparatus will be monitored every 4 weeks, after implantation, until week 24. Thereafter this assessment occurs every 8 weeks, and on the last visit (week 52).

d) Pain Assessments using the ISCIPDS:B and neuropathic rating scale will evaluate development of neuropathic pain syndromes.

The secondary hypothesis which concerns autonomic assessment will also take place during routine patient visits. Heart rate, blood pressure, sweating, body temperature and breathing will be classified as normal, abnormal, unknown, or unable to access. Within the abnormal category, sub-categories will be

specified: for heart rate, bradycardia, tachycardia or other dysrhythmias; for blood pressure, systolic blood pressure under 90 mm Hg, orthostatic hypotension, autonomic dysreflexia; for sweating, hyperhydrosis above lesion, hyperhydrosis below lesion, hyperhydrosis below lesion; for body temperature, hyperthermia, hypothermia; for breathing, requiring full ventilatory support, requiring partial ventilatory support, impaired not requiring ventilatory support. Lower urinary tract, bowel and sexual function will be scored on the following: awareness of need to empty bladder and ability to prevent urine leakage; sensation of need for bowel movement, ability to prevent stool leakage, voluntary anal sphincter contraction; genital arousal (psychogenic and reflex), orgasm, ejaculation (male), and sensation of menses (female).

Comprehensive testing sessions will analyze vagal and sympathetic influences on the cardiovascular system, measuring blood pressure and heart rate variability (power spectrum analysis) during sit-up or tilt-table challenge. However, if a subject is not able to tolerate the tilt table response exam to completion, he/she will not be required to fulfill this test at subsequent visits. The neurologist will decide whether it is recommended for subjects to undergo this assessment thereafter. Additionally, the test will not be required for subjects not expected to show autonomic dysreflexia because of their lower level of injury, as determined by the neurologist.

Assessment of motor and non-pain somatosensory function will be done during visits every 4 weeks. Clinical sensory testing will include Light Touch and Pin Prick tests defined in the ASIA standards [1]. The Beck Depression Inventory (BDI-1a) will also be used, to assess emotional function in neuropathic pain [4]. A score of 30 or above indicates severe depression. If BDI assessment suggests suicidal thoughts, the Columbia Suicide Severity Rating Scale will be used in consultation with a clinical psychologist.

16 ASSESSMENT OF TREND-TOWARD-EFFICACY

The trend towards efficacy of the intervention will be assessed from the following parameters:

a. AIS upper and lower extremity motor and sensory scores.

b. Pain Assessments: ISCI basic pain dataset, quantitative sensory testing and Self-report version of ISCI basic pain dataset.

c. Autonomic Assessments: BP, HR, tilt table response, sympathetic skin responses,

d. Quality of Life: Beck Depression Inventory (BDI-1a), Guy/Farrar Patient Global Impression of Change (PGIC).

17 STATISTICAL CONSIDERATIONS

17.1 Safety Analyses:

The analyses for safety will be mainly descriptive, focusing on trends for within-subject differences and changes in reported pain intensity during routine patient visits for the duration of the study. The expected outcome is stable, long-lasting change in the Pain Assessment Scale score from baseline to 44 weeks post-implant .All AEs and SAEs will be listed and their incidence compared to historical controls. The primary safety analysis will be conducted on all patient data when all 12 participants have completed the study.

Table 3: Surgical and equipment adverse events in DBS, based on 3 sources. The percentage per patient is given.

Information source	Reference 1 (n=133)	Reference 2 (n=124)	Reference 3 (n=468)

Lead fracture	6%	3%	0.4%
Intraoperative electrode migration	1.5%		
Late postoperative electrode migration	1.5%		
Implanted pulse generator migration	1.5%	4%	
Erosion	2.3%	3.2%	0.4%
Infection	1.5%	1.6%	1.3%
Erosion plus infection	1.5%		
Frequent external interference	1.5%		
Other		8.9%	0.02%
TOTAL	17.3%	17.7%	2.3%

Reference 1. Blomstedt P, Hariz MI. (2005. Hardware-related complications of deep brain stimulation: a ten year experience. Acta Neurochir (Wien). 147:1061-4.

Reference 2. Schuepbach WM, et al. (2013) Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med. 368: 610-22.

Reference 3. Experience of functional neurosurgery group (J. Jagid, B. Gallo, C. Luca) at the University of Miami (unpublished)

Safety will not primarily be evaluated statistically.

In addition to the continual monitoring of adverse events, safety analyses will use generalized linear models. The main dependent variable of interest is the Numeric Rating Scale (NRS) score for pain. Additionally there will be a fairly large number of dependent variables derived from assessments of other symptoms. Distributions will be modeled as binomial (yes=1 or no=0) or multinomial (e.g., score =1, 2, or 0) or normal (e.g., heart rate peak power after tilt, quantitative sensory thresholds). Less frequently, a Poisson distribution will be appropriate (e.g., number of times the patient reports autonomic dysreflexia in a given period). An appropriate link function will be chosen for each assumed distribution. Covariates to be considered are injury level, injury completeness and electrode configuration. The hypotheses to be tested for any variable (using the above factor coding) is that B<>A, C<>B, D<>B and D<>C. Marginal means can be used for this (except in multinomial examples, when main effects must suffice). Some participants may lack data from one condition (if they immediately opted for continuous high-level stimulation after the initial untreated period). If the continuous treatment is stopped soon after it starts, only the placebo effect (A<>B) will be available. Representative independent variables from each type of symptom will be further explored by discriminant analysis, which can confirm that one or more treatment condition represents a distinct state in the multivariate outcome space.

17.2 Efficacy Analyses:

To test the core hypothesis and secondary outcome measures, the analysis (descriptive) for efficacy trends will be conducted on the baseline through 52 weeks of data collection for all twelve (12) participants enrolled.

The one-minute recordings of local fields potentials from the bilateral or unilateral contacts PAG/PVG by the PC+S device will be analyzed in the time domain (autocorrelations and inter-lead cross-correlations) and the frequency domain (power in alpha, beta, gamma and delta EEG bands). Peaks in spectra or in auto- or cross-correlations will be examined for correlations with pain level (analgesia obtained) for each contact or pair of contacts. The potential ability shown by these results for usefulness in electrode targeting of future subjects (with pain from SCI or other causes) will be evaluated. That is, their

predictions of efficacy will be evaluated. These preliminary findings will be considered in the planning of studies with larger subject populations with pain of adequate statistical power.

17.3 Power Analyses:

This study is to be conducted for a period of three (3) years, starting from when the first subject is enrolled. As this is an open label safety study without a control group, no statistical analyses (other than descriptive) are proposed.

While a formal power analysis is not warranted, analysis of statistical power could be based on ASIA motor scores, whose variability has been most thoroughly detailed in the literature. This score ranges between 0 and 100. Data from a large-scale drug study on SCI showed that a 10-point change will reach a significance level of 0.05 if the number of patients with chronic cervical or thoracic injuries classified as ASIA A or B is ≈8 [51]. Recovery of sensory scores is typically more than 10%. Thus, the population size (n=12) should therefore have sufficient power for many planned statistical tests, especially since participants will serve as their own controls.

17.4 Missing Data

Although every attempt will be made to avoid missing outcome data, missing data is anticipated with any longitudinal study. The missing data can be defined as intermittent or dropout. Although every effort will be made to prevent participants from missing visits or dropping out of this study, it is possible that some of the measurements planned over the 52 weeks will be missing. The impact of missing data will be examined by comparing means and standard deviations for participants that have and do not have the relevant missed visit data. The reason for missing data will be fully examined to confirm this assumption.

Missing data will be imputed using regression methods.

17.5 Participant Attrition

Because of the lengthy 44-week follow-up, efforts will be made to minimize the number of participants lost to follow-up by developing good rapport, making the participant feel comfortable with the research staff and having regular correspondence between assessments. To maintain contact and continued willingness for study participation at each visit participants will provide their current address and phone number, pager numbers, and e-mail address as well as contact information for at least two individuals who live outside of their household yet are likely to know their whereabouts. Contact information and contact history will be entered into an electronic database allowing regular review and update.

18 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator agrees that qualified representatives of the Sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records (CRFs, source data/documents, etc.) pertinent to the clinical study as permitted by the regulations. Patients will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the patient will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) will be included in the informed consent document:

> *Representatives of regulatory agencies, IRB/IECs, the Sponsor, and your personal physician may review your medical records and all information related to this study as permitted by law. Identifying information will not appear on any record received by the Sponsor. Your identity will remain confidential unless disclosure is required by law.*

19 QUALITY CONTROL AND QUALITY ASSURANCE

19.1 Quality Control and Assurance Checks

a. Before enrolling any patients in this study, the Study Monitor and the Investigator will review the protocol, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs.

b. The Medical Monitor(s) will review the data for safety information; the Study Coordinator will review the data for legibility, completeness, and logical consistency.

c. Additionally, the Study Coordinator will identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Queries for data clarification or correction are forwarded to the investigator for resolution. A sample set of records will be fully audited against the corresponding CRFs.

19.2 Study Conduct

a. This study will be conducted in accordance with the IRB/FDA-approved protocol, and applicable regulations constituting Good Clinical Practices.

19.3 Monitoring of the Study

Monitoring will be conducted by the University of Miami's Clinical Research Operations and Regulatory Support Quality Control (CRORS QC) office. Site visits are made before the study begins, at regular intervals during the study, and at the study closeout. Communication by telephone, mail and e-mail may be used as needed to supplement site visits. The Investigator and study personnel will cooperate with the Sponsor, provide all appropriate documentation, and be available to discuss the study. The purpose of the site visits is to verify the following:

i. Adherence to the protocol. (The Investigator will not deviate from the protocol without prior written approval of Sponsor, except in emergencies. For medical emergencies, approval of a protocol deviation is not required, but Sponsor must be notified as soon as possible.)

ii. The completeness and accuracy of the CRFs and the device dispensing and inventory record. (Adequate time and space for these visits shall be allocated by the Investigator.)

iii. Compliance with regulations. The verification will require comparison of the source documents to the CRFs.

19.4 Protocol Deviations

Protocol deviations will be reported on the CRF, and will also be identified in data review by the Study Coordinator. Any deviation to the protocol that may have an effect on the safety or rights of the participant or the integrity of the study will be reported to the University of Miami Human Subject Research Office (UM HSRO) and FDA as soon as the deviation is identified.

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be documented and appropriately summarized.

19.5 Progress Reports

The PI will distribute bi-annual progress reports to the Funding Sponsor, the Miami Project to Cure Paralysis, communicating enrollment data, adverse events, and any outstanding issues or other relevant information. At the time of the IRB renewal the PI will submit in writing the frequency of the data monitoring, a summary of adverse events, other external factors or relevant information that might have an impact on the safety or ethics of the study, final conclusions regarding changes

to the anticipated risk/benefit ratio to study participation, and final recommendations related to the continuation, alteration, or termination of the study.

19.6 Audits and Inspections

The conduct of the study (including the selected CRFs and corresponding patient source records) will be periodically audited for compliance with FDA's Good clinical Practices and ICH-E6. Such audits will be conducted at least twice in the course of the Study, and will be conducted by the UM Office of Research Compliance & Quality Assurance (RCQA) auditors.

The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to the Sponsor and the IRB.

20 ETHICS

20.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The clinical protocol will be submitted to and approved by the University of Miami Human Subject Research Office (UM HSRO) and the FDA, and will not be initiated until written notification of approval of the research project is issued. Accurate and complete study records will be maintained and made available to representatives of the UM HSRO and FDA as a part of their responsibility to protect human subjects in research.

20.2 Informed Consent

a. Participants with chronic spinal cord injury will be recruited from consecutive patients including men and women. Only participants who can provide their own Informed Consent without proxy will be included in the study. The discussions will take place in an area where privacy and confidentiality can be respected. The participant will be given sufficient time to comprehend the research and discuss the study before making a decision. The researcher will clearly explain the background/purpose, voluntary nature, commitment, risks, benefits, alternatives, and other elements, and will answer any questions. If the participant agrees to participate, written Informed Consent will be obtained and study intervention/treatment protocol will ensue.

b. The device implantation surgery informed consent will be obtained 2-3 days prior to scheduling the procedure.

c. It will be explained to the patient that they have the right to refuse to take part and/or withdraw from this study at any time without penalty or loss of care. Their ongoing medical care will not be affected by the decision to take part or not take part in this study. Participants who take part in the study will receive the same level of care that is considered the community standard. Patients who do not to take part in the study will also receive community standard care.

20.3 Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and the applicable regulatory requirements.

20.4 Participant Confidentiality

To maintain participant confidentiality, all study documents and files will use an anonymous study identification number to identify participants and only the study coordinator will maintain linkages, and have access to, subject identities. Local computer storage of data is password protected and located within a hospital- or institute-based firewall. Study data will be stored in the clinical research office at the Lois Pope Life Center.

The Data Safety Monitoring Plan to maintain confidentiality is as follows.

a. The data will be stored for at least ten (10) years.

b. All physiologic and neuropsychological data is coded with a unique identifying number, different from the subject's medical record number or social security number, to maintain confidentiality, in order for these to be matched to the samples. The study coordinator is responsible for maintaining this code. The demographic information of the subject initially required to code with is password protected on his/her computer and is within a locked office.

c. All signed consents and study data are stored within a locked filing cabinet in a locked office for which the PI will have oversight. Only personnel listed on study protocols will have access to study data. However, pertinent study data will be shared with a subject in cases where the subject could possibly benefit medically or otherwise from the data, or upon their request.

d. Any findings that increase risks to participants will also be shared with all study participants.

e. Study data will also be made available to the Funding Sponsor, The Miami Project to Cure Paralysis and the FDA for audit.

f. Study data may also be made available to consultants hired by the Miami Project to Cure Paralysis/Miller School of Medicine bound by written confidentiality for the specific purpose of providing oversight on the project.

21 DATA HANDLING AND RECORDKEEPING

21.1 Case Report Forms

a. Where possible, data will be documented in source documents initially and then recorded on CRFs. Dark indelible-ink pens (preferably black-ink ballpoint pens) shall be used.

b. The originals of the CRFs plus one additional copy must be returned to the Sponsor; the PI must retain a copy of the CRFs for his/her file.

c. CRFs and other pertinent records are to be submitted to the Sponsor during and/or at completion or termination of the study.

d. The Investigator also must submit all incomplete CRFs that document patient experience with the study device, including retrievable data on patients who withdraw before completion of the study.

e. Laboratory results and ECG results will be processed using electronic data provided from the centralized organizations and directly submitted to the data management group. Any additional types of data that will be recorded directly into the CRF shall be listed in Section 10.3.8 of this protocol.

21.2 The Study Coordinator

The PI will monitor the progress of the research study with the assistance of a Study Coordinator. Data will be entered into Case Record Forms (CRF) at the study site within 5 days of the data time-

point**,** and the Study Coordinator will review the accuracy of the entered data by comparison with participants' medical records within thirty (30) days. Potential discrepancies will be flagged and checked/corrected by study site personnel.

21.3 Adverse Event Reporting

The Investigator agrees to report all AEs to the Sponsor as described in the Adverse Events Reporting section, Appendix 1. Furthermore, the Investigator is responsible for ensuring that any Co-investigator or Sub investigator promptly brings AEs to the attention of the Investigator. The Investigator also is responsible for informing the participating IRB/IEC of any SAEs.

21.4 Protocol Amendments

a) Any significant change in the study protocol will require an amendment. In addition, major modifications to the research protocol and any modifications that could potentially increase risk to participants will be submitted to the FDA for approval prior to implementation.

b) The Investigator and the Medical Monitor indicate their approval of significant changes to the protocol or CRFs by signing the approval page of the amendment. Once the Sponsor has approved a protocol amendment, the Investigator shall submit it to the IRB/IEC for written approval. The Sponsor submits a copy of the protocol amendment to the appropriate regulatory agency/agencies. A protocol amendment may be implemented after it has been approved by the IRB/IEC.

c) A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within five (5) working days, and submitted to the appropriate regulatory agency in the required time frame.

d) Minor amendments (including minor changes to CRFs) will be submitted with the continuing review report to the UM HSRO for acceptance.

21.5 Final Study Report

a) The Investigator must complete a report notifying the IRB/IEC of the conclusion of the clinical study. This report should be made within three (3) months of completion or termination of the study.

b) The final report sent to the IRB/IEC must also be sent to the Sponsor and, along with the completed CRFs, constitutes the final summary to the Sponsor, thereby fulfilling the Investigator's regulatory responsibility.

21.6 Records Retention

a) The Investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those documents defined by GCP as essential documents, for the longer of: (a) 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug or (b) such longer period as required by applicable global regulatory requirements.

b) At the end of such period, the Investigator shall notify the Sponsor of the intent to destroy all such material.

c) The Sponsor shall have 30 days to respond to the Investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

22 FINANCING AND INSURANCE REGARDING PATIENT INJURY

In general, if a patient is injured as a direct result of the study device, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the patient's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation. Where applicable, the Sponsor will take specific national insurance.

23 PUBLICATION POLICY

All data will be summarized and analyzed. The Principal Investigators will prepare a clinical narrative. The Principal Investigators will prepare abstract submissions to an appropriate research meeting and a manuscript for submission to a peer-reviewed journal. The publication policies of The Miami Project to Cure Paralysis and Miller School of Medicine follow those recommended by the Association of American Medical colleges and the Institute of Medicine. The trial will be fully registered according to International Committee of Medical Journal Editors (ICMJE) standards within 21 days of its outset in http://clinicaltrials.gov/.

24 APPENDICES

24.1 Appendix 1 - Description of Adverse Event Reporting (following page)

24.2 Appendix 2 – Protocol References

24.1 APPENDIX 1 -- ADVERSE EVENTS REPORTING

1. Definitions

1.1. An **Adverse Event (AE)** [a.k.a. "adverse experience"] is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations

occurring in a human being participating in a clinical study with a Sponsor study device, regardless of causal relationship. This includes the following:

- Any clinically significant worsening of a preexisting condition.
- Any recurrence of a preexisting condition.
- An AE occurring from excessive output of a Sponsor study device whether accidental or intentional (i.e., an amplitude higher than that prescribed by a clinical neurophysiologist).
- An AE that has been associated with the discontinuation of the use of a Sponsor study device.

Note: A medical procedure is not an AE, but the reason for a procedure may be an AE.

1.2. A **Preexisting Condition** is a clinical condition (including a condition being treated) that is diagnosed before the patient signs the informed consent form and that is documented as part of the patient's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency are used to determine whether an event is a treatment-emergent AE (TEAE). An AE is considered to be treatment emergent if:

- it was not present when the active phase of the study began and is not a chronic condition that is part of the patient's medical history, or
- it was present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increased during the active phase. The active phase of the study begins at the time of the first use of the study device.

1.3. A **Serious Adverse Event (SAE)** is any AE occurring at any dose (voltage output) that results in one (1) or more of the following outcomes:

- Death.
- Life threatening situation (see below).
- Inpatient hospitalization or prolongation of an existing hospitalization (see below).
- Persistent or significant disability or incapacity (see below).
- Congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization. If there is any doubt whether the information constitutes an AE or SAE, the information is treated as an AE or SAE.

1.4. A **Life Threatening Adverse Event** is any AE that places the patient at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred.

1.5. **Hospitalization** is to be considered only as an overnight admission. Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating Investigator should not report hospitalization or prolongation of hospitalization on a CRF. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- Day or night survey visits for biopsy or surgery required by the protocol.
- Hospitalization or prolongation of hospitalization as part of a routine procedure followed by the study center (e.g., stent removal after surgery).
- In addition, a hospitalization planned before the start of the study for a preexisting condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the study).

1.6. **Disability** is defined as a substantial disruption in a person's ability to conduct normal life functions.

2. Timing for Reporting Serious Adverse Events

2.1. Any SAE, regardless of causal relationship, must be reported to the Sponsor's Medical Monitor (or a designated affiliate) immediately (i.e., within 24 hrs). A completed Serious Adverse Event Form must be faxed to the number indicated at the front of the clinical protocol no later than 24 hours after the investigator becomes aware of the SAE. A phone call should be made to confirm that the SAE fax was received. Compliance with this time requirement is essential for the Sponsor to comply with regulatory obligations.

2.2. Follow-up information relating to an SAE must be reported to a Sponsor Medical Monitor (or an affiliate or designee) within 24 hours of receipt by the Investigator by faxing a completed serious adverse event form to the number indicated in the front of this protocol and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

2.3. Any emergency must be reported to a Sponsor Medical Monitor (or an affiliate or designee) immediately (within 24 hours) by contacting a Medical Monitor listed in the front of this protocol.

2.4. For all other inquiries and information about this study, contact Miami Project to Cure Paralysis at the phone number listed in the front of the clinical protocol.

3. Reportable Events/Information

3.1. An AE or SAE that occurs between the time that the patient signs the informed consent form through thirty (30) days from the patient's last dose (voltage output), regardless of study device or protocol relationship should be reported. This includes events that emerge during the screening and pre-treatment run-in periods.

- All AEs and SAEs will be recorded on source documents and recorded on CRFs.
- All AEs and SAEs that occur after the screening period will be recorded on the CRFs.
- The Sponsor Medical Monitor must instruct the investigator to follow up as is medically necessary on all AEs, SAEs, and other reportable events until the event has subsided or values have returned to baseline, or in case of permanent impairment, until the condition stabilizes.

3.2. For SAEs: The investigator will provide all documentation pertaining to the event (e.g., additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to the Sponsor Medical Monitor in a timely manner. Reports relative to the patient's subsequent course must be submitted to the Sponsor until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

4. Post-study SAEs related to device include any abnormal biological or vital signs values that are considered clinically relevant by the Investigator. These must be reported in the same time frame and following the same process as for an AE or an SAE

4.1. The Investigator managing the excessive voltage may order any additional test(s) he or she thinks is necessary to manage the patient properly.

5. Recording and Reporting

5.1. At each required study visit, all AEs that have occurred since the previous visit must be documented and recorded in the Adverse Event Record of the patient's CRF. The information recorded should be based on the signs or symptoms detected during the physical examination and clinical evaluation of the patient. In addition to the information obtained from those sources, the patient should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

5.2. The following AE information must be included (when applicable):

- the specific condition or event and direction of change;
- whether the condition was preexisting (i.e., an acute condition present at the start of the study or history of a chronic condition) and, if so, whether it has worsened (e.g., in severity and/or frequency);
- the dates and times of occurrence; severity; causal relationship to study device; action taken; and outcome.

5.3. The causal relation between an AE and the study device will be determined by the investigator on the basis of his or her clinical judgment and the following definitions:

- **Definitely related:** Event can be fully explained by use of the study device.
- **Probably related**: Event is most likely to be explained by use of the study device rather than the patient's clinical state or other agents/therapies.
- **Possibly related**: Event may be explained by use of the study device or by the patient's clinical state or other agents/therapies.
- **Probably not related**: Event is most likely to be explained by the patient's clinical state or other agents/therapies, rather than the study device.
- **Definitely not related**: Event can be fully explained by the patient's clinical state or other agents/therapies.

5.4. When assessing the relationship between use of a study device and an AE, the following should be considered:

- Temporal relationship between use of the study device and the AE.
- Biological plausibility of relationship.
- Patient's underlying clinical state or concomitant agents and/or therapies.

5.5. SAEs that are not study device related may nevertheless be considered by the participating Investigator or the Medical Monitor (or designee) to be related to the conduct of the clinical study, i.e., to a patient's participation in the study. For example, a protocol-related SAE may be related to a procedure required by the protocol.

5.6. The following definitions should be used when determining the severity of an AE. Please note that there are some cases in which removal of study device may be appropriate.

- **Mild (grade 1):** The AE is noticeable to the patient but does not interfere with routine activity. The AE does not require discontinuing use or reducing the voltage output of the

study device.

- **Moderate (grade 2):** The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the voltage output but not discontinuing use of the study device.
- **Severe (grade 3):** The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing use or reducing the voltage output of the study device.
- **Life Threatening (grade 4):** The AE requires discontinuing use of the study device. The patient is at immediate risk of death.

24.2 APPENDIX 2 – PROTOCOL REFERENCES

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