CLINICAL PROTOCOL (version 10.01.2019)

Title: **Deep brain stimulation (DBS) in patients with refractory chronic neuropathic pain**

Protocol: **NCT03029884**

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Protocol Synopsis

Title	Deep brain stimulation (DBS) in patients with refractory chronic neuropathic pain
Study Phase	Phase I
Device(s)	**Device Information:** Devices to be used in this study are grouped below according to FDA approval. All are Medtronic Devices. **Investigational** • Activa PC+S implantable pulse generator, Model 37604 • Sensing Programmer Model 8181 for Activa PC+S • Sensing Programmer Software Model 8180 for Activa PC+S • Intercept Patient Programmer, model 37441 • Lead extension Model 37087 • Nexus-D (vD3) / E Systems • Nexus-D Application Programming Interfaces (v1.5) • Nexus-E Activator Model 4NR005 **Approved for other indications** • Medtronic Resume II paddle electrode model 3587A • Medtronic Resume II paddle electrode model 031930 • N'Vision Clinical Programmer Model 8840 • Clinician Programmer Software Model 8870 • Patient Programmer Model 37642 • Patient Programmer Antenna Model 37092 • Medtronic Lead Model 3389S/ 3387S / 3391S • External Neurostimulator 37022 • Lead extension model 37086
Indication	Adults with refractory chronic neuropathic pain, specific to phantom limb, spinal cord injury or post-stroke, who have failed standard medical pain management (e.g. more than two pain medications from different classes, spinal injections) for one year or more.
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Data Safety Monitor Board (DSMB)	Dr. Line Jacques, MD, a neurosurgeon and chief of peripheral nerve and pain surgery at UCSF, not directly involved in this study, will lead the DSMB that will review the study data and provide guidance on a regular basis. Dr. Line Jacques, MD, UCSF, 505 Parnassus Ave. Rm. M779, San Francisco, CA 94143-0112
Treatment	Deep-brain stimulation of paired brain regions related to neuropathic pain, cingulate cortex and orbital frontal cortex.
Study Sites	University of California, San Francisco 505 Parnassus Ave 675 Nelson Rising Lane San Francisco, CA 94143 San Francisco, CA 94143
Study Design	This is a single-center study of the effectiveness of open- and closed-loop DBS paradigms in the treatment of chronic neuropathic pain disorders that are refractory to current treatment options (e.g. two or more pain medications from different classes, spinal injections). Our primary objectives are to: 1) Determine the neural correlates of increased pain states in patients with chronic pain in order to enable targeted DBS treatment 2) Provide pain relief with neural stimulation 3) Establish the efficacy of open-loop and closed-loop DBS paradigms. DBS electrodes will be inserted into regions of the brain related to pain processing. After implantation of electrodes, study patients will undergo three phases of assessment. In phase 1, patients will undergo ambulatory monitoring (~6 months) of their pain states linked to recordings of local field potentials (LFPs) in pain-processing regions. Stimulation will not be enabled during this period. This phase will be conducted in both the outpatient office setting and the patient's home environment. Throughout this period, data will be analyzed to develop a predictive model of increased pain states and to guide precision DBS treatment. In phase 2, we will determine the stimulation parameters that optimally reduce the level of pain for each patient, in clinic daily, for 1-2 weeks. We will then randomly assign patients to 3-week periods of stimulation ON / stimulation OFF. We anticipate this phase will last approximately 6 months and that stimulation will be conducted in the office as well as the home setting. Patients will be under close monitoring, with frequent in-clinic appointments.

	In phase 3, we will determine differences in pain relief efficacy for at-home open-loop versus closed-loop stimulation parameters (single-blind study). Patients will be under close monitoring, with frequent in-clinic appointments. In phase 1, if data of sufficiently high quality is collected before the 6 month phase period ends, and a predictive biomarker is found before the 6-month phase period ends, the patient can accelerate to the next phases of the study to help ensure a rapid positive clinical outcome. Similarly, the patient may accelerate from phase 2 to phase 3 before the 6-month period ends to ensure rapid positive clinical outcomes.
Objectives	In ten patients with chronic pain refractory to standard medical treatment, we will implant DBS electrodes in brain regions related to pain processing (phantom limb, spinal cord injury and post-stroke pain patients implanted in cingulate and orbital frontal cortex). We will connect these electrodes to an implantable pulse generator that stores field potential data in addition to delivering stimulation (Medtronic Activa PC+S). At multiple time points post-implantation (in our clinic and the patient home), we will record LFP data in conjunction with data regarding pain states. We will also record LFP data in conjunction with quantitative sensory testing (QST) of pain thresholds. Together, these data collections will allow us to identify neurophysiological correlates of pain and then use these signals to set stimulation parameters to disrupt pain-related neural activity, thereby reducing pain states for patients. Hypotheses: 1) Local field potentials recorded using DBS electrodes can predict the transition to an elevated pain state. 2) Open-loop stimulation in response to elevated pain states will reduce duration and/or intensity of the pain state. 3) Closed-loop stimulation may be more effective in treating pain symptoms than open-loop stimulation owing to temporal targeting and avoidance of potential side effects.
Patient Population	Study subjects will be adults with refractory chronic neuropathic pain. <u>Inclusion Criteria</u>. • Age ≥ 21 years • Clinical diagnosis of post-stroke pain (thalamic pain), spinal cord injury or phantom limb pain with allodynia or dysesthesia with pinprick anesthesia or hypoesthesia on the affected hemibody or limb (anesthesia dolorosa). • <u>For Post-Stroke Pain</u>: Stroke of ischemic etiology only. MRI done within one year of the first visit showing a lesion that involves the contralateral brainstem, thalamus or cortex. The lesion will involve cortical-subcortical areas in topography consistent with sensory thalamocortical connections. This will include patients with infarcts in the territory of the middle cerebral artery or those with cavernous malformations. A more recent MRI may be required if the patient's condition changed within the previous year.

	• <u>For Phantom limb pain:</u> MRI done within one year not showing any contraindication to surgery such as mass, lesion, hemorrhage or other abnormality near target • <u>For Spinal Cord Injury pain:</u> MRI done within one year not showing contraindication to surgery such as mass, lesion, hemorrhage or other abnormality near target • One year or more of medically refractory severe pain (see below) • Average daily pain for the past 30 days reported as >5 on a 0-10 numeric rating scale (NRS) • Failure to respond adequately to at least one antidepressant, one anti-seizure medication and one oral narcotic with current stable doses of medications. • Ability to speak / read English • Capable of understanding and providing informed consent • Stable doses of pain medications (e.g. anticonvulsant drug, anti-depressants, and opioids etc.) • Women of childbearing age must be on regular use of an accepted contraceptive method(s). <u>Exclusion Criteria</u>. • Pregnancy or breast feeding • Inability to speak and / or read English • Inability to give informed consent • Significant cognitive impairment or Dementia (MoCA < 25) • Aphasia severe enough to limit the consent process or communication between the investigators and the patient. Patients with mild or recovering aphasia may be considered candidates at the discretion of the PI. • Active depression (BDI > 20) or other untreated or uncontrolled psychiatric illness (active general anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or personality disorders (e.g. multiple personality disorder, borderline personality disorder, etc.) or other neuropsychiatric conditions that evaluating psychiatrist would recommend exclusion of patient after neuropsychiatric evaluation. • Suicide attempt </= 12 months or imminent suicide risk • History of substance abuse in past 3 years. • Major medical co-morbidities increasing the risk of surgery including uncontrolled hypertension, severe diabetes, major organ system failure, history of hemorrhagic stroke, need for chronic anticoagulation other than aspirin, active infection, immunocompromised state or malignancy with < 5 years life expectancy • Inability to stop Coumadin or platelet anti-aggregation therapy for surgery and after surgery. Patients taking these medications will need to discuss the need/risk of continuing these medications with their physicians and the PI or study personnel may contact the treating physician(s) as well to discuss the risks of anticoagulation / antiaggregation therapy discontinuation. • Coagulopathy. Patients will be excluded unless assessed and cleared by hematology.

	• MRI (done within one year of the first visit) with significant abnormalities other than those associated with the neurological disorder causing chronic pain. • Implantable hardware not compatible with MRI or with the study. • Inability to comply with study follow-up visits • Previous ablative intracranial surgery for the management of the thalamic pain syndrome. • Previously implanted with deep brain stimulation system or any previously implanted device treatment involving brain stimulation • Major neurological disorder other than the one that led to the chronic pain including epilepsy, neurodegenerative condition or any history of seizure • Requires diathermy, electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) to treat a chronic condition • Has an implanted electronic device such as a neurostimulator, cardiac pacemaker or medication pump • Allergies or known hypersensitivity to materials in the Activa PC+S system (i.e. titanium, polyurethane, silicone, polyetherimide, stainless steel). • Pregnancy or lack of regular use of contraceptives. Patients who become pregnant after enrollment may be excluded from the study. Patients who become pregnant prior to the surgical implantation of the DBS systems will be excluded from the study. • Patients may be excluded from enrollment due to a condition that, in the judgment of the PI, significantly increases risk or reduces significantly the likelihood of benefit from DBS.
Sample Size	10 patients
Efficacy Assessments	<u>Primary Endpoints</u> • Pain intensity / relief visual analog scale • Thermal pain threshold testing with QST <u>Secondary Endpoints</u> • Neuropathic Pain Questionnaire • NIH PROMIS Global health and physical function scales • SF-36
Safety Assessments	• Physical examination at specified study visits (see Section 6.0) • Check of pulse generator stimulation parameters, impedance measurements, and battery voltage at all study visits • Surgical or nonsurgical protocol-defined adverse events as recorded on adverse events case report forms • Assessment of suicidality using the Columbia Suicide Severity Rating Scale, and assessment of changes in depression and anxiety using the Beck Depression and Anxiety Inventories, at all protocol-defined outpatient visits • Daily visits for up to 2 weeks at start of Phase 2 for optimizing stimulation parameters.

*Abbreviations: C-SSRS=Columbia Suicide Severity Rating Scale; BDI=Beck Depression Inventory; BAI=Beck Anxiety Inventory.

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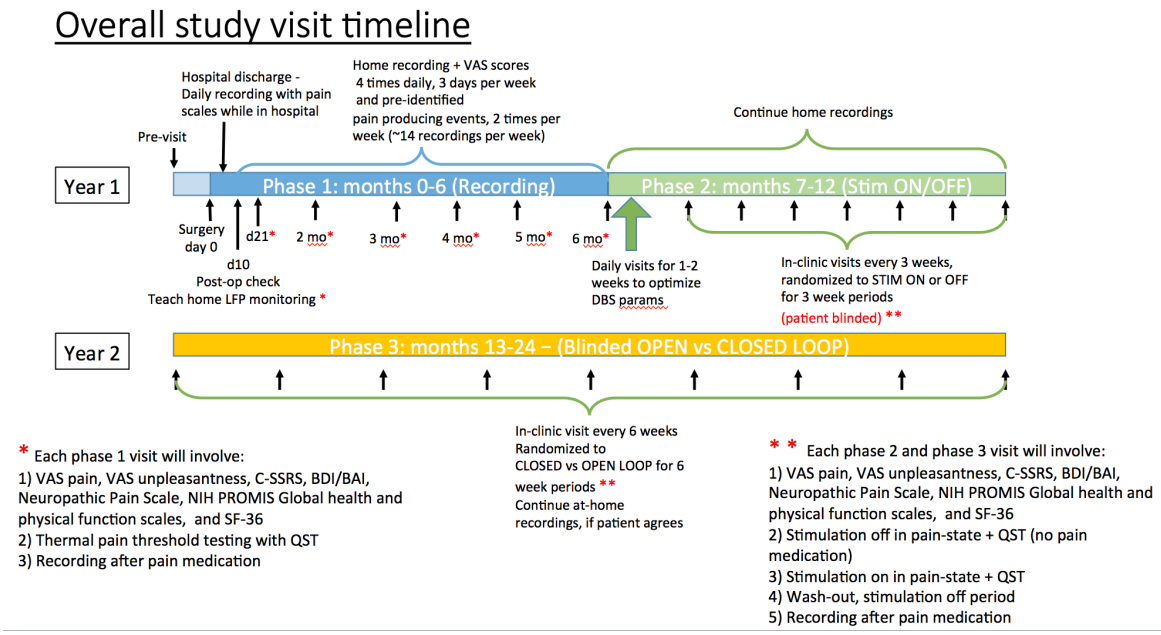
1.0 Investigational Plan

This is a single-center study of the neurophysiology of neuropathic pain disorders with several goals: (1) define the electrophysiological correlates of elevated pain states (i.e. abnormal LFP oscillatory activity), [120] determine the DBS parameters that can disrupt such abnormal oscillatory activity and acutely reduce this pain state, (3) integrate that biomarker of pain in a closed-loop DBS paradigm and (4) compare success rates of pain remediation for stimulation across pain etiologies.

In a cohort of 10 subjects, we aim to assess the feasibility of disrupting pain states using deep brain stimulation. Bilateral or unilateral surgical implantation of electrodes will be dependent on the etiology and specific clinical presentation of the patient's chronic neuropathic pain. For instance, chronic neuropathic pain patients with unilateral pain syndromes may only require unilateral implantation of each of the target sites [85], (i.e. two electrodes and 1 Activa PC+S pulse generator). However, patients with bilateral neuropathic pain symptoms may require bilateral implantation of both target sites (i.e. a total of 4 electrodes and 2 Activa PC+S pulse generator devices). Bilateral implantation of the anterior cingulate has been shown to alleviate pain with open-loop stimulation [93, 94]. Additionally, for the past 10 years, effective results of bilateral open-loop stimulation of the cingulate cortex have been reported for the treatment of depression utilizing Medtronic devices [142]. Lastly, preliminary safety and feasibility of two Activa PC+S device implants with two bilateral electrode implants is suggested by another clinical trial which currently uses a similar surgical design (two Activa PC+S devices implanted in the chest in the same patient, connected to bilateral thalamic and bilateral electrocorticography strips) [141].

The UCSF Institutional Review Board (IRB) has approved our investigational plan and protocol, in which we propose to conduct the testing in three phases for each subject, (see Figure: Overall study visit timeline).

Figure 3: Overall study visit timeline



Phase 1 – At-home recordings

In phase 1, patients will be implanted and undergo long-term ambulatory monitoring of their self-reported pain states along with recordings of LFPs from electrodes implanted in the cingulate and orbitofrontal paired regions (~6 months in duration, time period based on previous pain studies [2, 85], visits 6-10, approximately 1 visit per month, up to 10 visits, if needed). Neural activity from implanted electrodes will be simultaneously recorded, one lead per recording channel. During this time period, neural data in combination with pain state reports will be analyzed in order to identify biomarkers of the pain experience and develop a predictive model of increased pain. Importantly, although recruitment will only include patients who are treatment-resistant to pain medication, patients will likely be on medication regimens for pain relief. These will continue to be managed by the patient's regular pain management team (i.e. will be independent of this study). We will closely monitor the medication regimen and any changes to the regimen. Patients will be asked to record activities at least 3 days a week at the following times:

a. Immediately after waking up in the morning
b. 30 mins post medication use
c. afternoon between 1200 - 1400 pm
d. immediately before bedtime

Also, twice a week, patients will be asked to record during pre-identified activities that exacerbate pain (e.g. bending, climbing stairs, etc.). Patients will also be asked to wear a FitBit or similar activity monitor and upload their anonymized data (i.e. no personal health information shared).

Phase 1 – In-clinic sessions

In clinic sessions will also occur in Phase 1, occurring approximately every 3 weeks, taking the measures of VAS pain, VAS unpleasantness, C-SSRS, BDI/BAI, Neuropathic Pain Questionnaire, NIH PROMIS Global health and physical function scales and SF-36. Baseline LFP recordings will also be taken from ~2 minutes. At the study visits from week 3 onwards, we will also include

Quantitative sensory testing (QST) with the Medoc device. Using cold and heat, we will test sensory perception and pain thresholds 3 times each in the aspect of both hands (contra and ipsi lateral to pain). The device will slowly increase/ decrease temperature until the patient reports sensation (1st endpoint) and then pain (2nd endpoint) which will be recorded. Heat and cold perception and pain thresholds will be tested, with the patient record VAS for pain threshold on each trial. Three consecutive trials will be conducted in each session to establish reliability. LFP recordings will be recorded during the QST sessions with clinician-initiated recording. A computerized cognitive-attention task will be performed. We will test patient reaction time and short-term memory recall using a computerized task, requiring patients to respond to tasks by pressing a keyboard key and verbally recalling words during the memory task. Three consecutive trials will be conducted within a single session with the task order shuffled to establish test reliability. LFP recordings will be recorded during the cognitive-attention task sessions with clinician-initiated recordings. We will also conduct an anticipatory anxiety task where participants will be provided with a non-painful, random buzzing stimulation on the finger paired with a continuous auditory cue indicating which period of time will contain random irritating stimulation. Finger stimulation using a BIOPAC stimulation will be titrated up to a non-painful, highly irritating voltage before each task session. We will be collecting LFP recordings throughout this task to record pain anticipation signals. LFP recordings will also be recorded during pre-identified painful activities or movement and after painful activity with VAS scores recorded during these times as well. Patients will be asked to avoid pain medication two hours prior to their appointments. Post-testing, patients will then take medications and 2-minutes of recording will be obtained 15-minutes after pain medication is given. We may also use electroencephalography (EEG) to record brain data during some clinic visits to support biomarker identification.

A predictive biomarker of pain will be discovered in phase 1 from data collected with at-home and in-clinic recording sessions. This biomarker discovery will be implemented in Phase 2. In phase 1, if data of sufficiently high quality is collected before the 6-month phase period ends, and a predictive biomarker is found before the 6-month phase period ends, the patient can accelerate to the next phases of the study to help ensure a rapid positive clinical outcome.

Phase 2

In the first two weeks of Phase 2, patients will be seen daily for up to two weeks to optimize DBS parameters (visits 11-24), based on biomarker discovery from Phase 1. EEG may be used during this phase for safety, to ensure that subclinical seizure activity is not present during stimulation. If data-collection during the initial two-week period is curtailed for any reason, additional DBS optimization visits may be scheduled so as to sufficiently optimize the biomarker and stimulation settings to enable closed-loop stimulation.

Patients will then have closed-loop stimulation enabled for at-home stimulation, with follow-up clinic visits scheduled every 3 weeks. Stimulation will be enabled or disabled in an ON/OFF state with patient blinded to stimulation status to test for potential placebo / sham effects. In addition to at-home reporting (similar to Phase 1), efficacy of stimulation will be tested every three weeks in-clinic. Additional in-clinic testing of stimulation-related analgesia efficacy and mechanism of action will be done using acute administration of intranasal (4mg/0.1ml, up to two doses), intramuscular (0.4mg/1ml) or IV naloxone (0.4mg/1ml), or saline as control. Study team will assist in administering naloxone before and during analgesic stimulation ON/OFF. Patients and study team will be blinded to what is being provided. Patients who are participating in pain management using opioids will be excluded from performing this study procedure. Phase 2 will last approximately 6 months in duration, time period based on previous unpublished observations in human Parkinson's

patients from our group [143] and published non-human primate observations [58]. Phase 2 in-clinic visits occurring every 3 weeks will test the following:

1) VAS pain, VAS unpleasantness, C-SSRS, BDI/BAI, Neuropathic Pain Scale, NIH PROMIS Global health and physical function scales, and SF-36
2) Baseline LFP
3) Stimulation off + QST (no pain medication)
4) Stimulation on + QST (no pain medication)
5) Stimulation off + anticipatory anxiety task
6) Stimulation off + anticipatory anxiety task
7) Stimulation off + cognitive-attention task
8) Stimulation off + cognitive-attention task
9) Stimulation off + naloxone
10) Stimulation on + naloxone
11) Wash-out, stimulation off period
12) LFP recording after painful activity
13) Recording after pain medication

Phase 2 will test the effectiveness of closed-loop stimulation in comparison to no-stimulation. In phase 3, the effectiveness of closed-loop stimulation will be tested in comparison to open-loop stimulation settings. If data of sufficiently high quality are collected before the 6-month phase period ends in Phase 2, depending on pain relief symptoms, the research team may accelerate phase 2 to phase 3 before the 6-month period ends to ensure rapid positive clinical outcomes.

Phase 3

In phase 3, patients will continue with at-home stimulation with either personalized closed-loop or traditional open-loop stimulation strategies enacted via their implanted system. Patients will be blinded to the stimulation strategy in which they are assigned. Assignment of open-loop or closed-loop will be randomized and occur in 6-week time periods, with each patient serving as his or her control as to which stimulation treatment is more effective. EEG may be used during this phase for safety, to ensure that subclinical seizure activity is not present during stimulation.

During this phase, patients will be monitored closely, with daily at-home phone calls and frequent in-clinic appointments. This phase of the study will last approximately 1 year (time line based on previous published reports [2, 85, 94], with in-clinic appointments occurring approximately every 6 weeks.

In-clinic appointments will consist of the following:
1) VAS pain, VAS unpleasantness, C-SSRS, BDI/BAI, Neuropathic Pain Scale, NIH PROMIS Global health and physical function scales, and SF-36
2) Baseline LFP
3) Stimulation off + QST (no pain medication)
4) Stimulation on + QST
5) Stimulation off + anticipatory anxiety task
6) Stimulation on + anticipatory anxiety task
7) Stimulation off + cognitive-attention task
8) Stimulation off + cognitive-attention task
9) Stimulation off + naloxone
10) Stimulation on + naloxone

11) Wash-out, stimulation off period
12) LFP recording after painful activity
13) Recording after pain medication
14) Closed-loop DBS being turned to open-loop stimulation setting, previous open-loop stimulation being turned to closed-loop DBS setting, randomized, or turning stimulation off for a wash-out period of up to 2-months.

Phase 3 will inform the research team as to whether open-loop or closed-loop stimulation is most effective on a patient-by-patient basis.

At the end of the study, patients will have the option for 1) continued active closed-loop or open-loop stimulation with the current implanted device, with in-clinic appointments, 2) discontinuing stimulation with the device turned off or 3) having the device removed.

2.0 Patient Eligibility

Inclusion Criteria.

- Age ≥ 21 years
- Clinical diagnosis of post-stroke pain (thalamic-pain), spinal cord injury or phantom limb pain with allodynia or dysesthesia with pinprick anesthesia or hypoesthesia on the affected hemibody or limb (anesthesia dolorosa).
- For Post-Stroke Pain: Stroke of ischemic etiology only. MRI done within one year of the first visit showing a lesion that involves the contralateral brainstem, thalamus or cortex. The lesion will involve cortical-subcortical areas in topography consistent with sensory thalamocortical connections. This will include patients with infarcts in the territory of the middle cerebral artery or those with cavernous malformations. A more recent MRI may be required if the patient's condition changed within the previous year.
- For Phantom limb pain: MRI done within one year not showing any contraindication to surgery such as mass, lesion, hemorrhage or other abnormality near target
- For Spinal Cord Injury pain: MRI done within one year not showing contraindication to surgery such as mass, lesion, hemorrhage or other abnormality near target
- One year or more of medically refractory severe pain (see below)
- Average daily pain for the past 30 days reported as >5 on a 0-10 numeric rating scale (NRS)
- Failure to respond adequately to at least one antidepressant, one anti-seizure medication and one oral narcotic with current stable doses of medications.
- Ability to speak / read English
- Capable of understanding and providing informed consent
- Stable doses of pain medications (e.g. anticonvulsant drug, anti-depressants, and opioids etc.)
- Women of childbearing age must be on regular use of an accepted contraceptive method(s).

Exclusion Criteria.

- Pregnancy or breast feeding
- Inability to speak and / or read English
- Inability to give consent
- Significant cognitive impairment or Dementia (MoCA < 25)
- Aphasia severe enough to limit the consent process or communication between the investigators and the patient. Patients with mild or recovering aphasia may be considered candidates at the discretion of the PI.
- Active depression (BDI > 20) or other untreated or uncontrolled psychiatric illness (active general anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or personality disorders (e.g. multiple personality disorder, borderline personality disorder, etc.) or other neuropsychiatric conditions that evaluating psychiatrist would recommend exclusion of patient after neuropsychiatric evaluation.
- Suicide attempt </= 12 months or imminent suicide risk
- History of substance abuse in past 3 years
- Major medical co-morbidities increasing the risk of surgery including uncontrolled hypertension, severe diabetes, major organ system failure, history of hemorrhagic stroke, need for chronic anticoagulation other than aspirin, active infection, immunocompromised state or malignancy with < 5 years life expectancy
- Inability to stop Coumadin or platelet anti-aggregation therapy for surgery and after surgery. Patients taking these medications will need to discuss the need/risk of continuing these medications with their physicians and the PI or study personnel may

contact the treating physician(s) as well to discuss the risks of anticoagulation / antiaggregation therapy discontinuation.

- Coagulopathy. Patients will be excluded unless assessed and cleared by hematology.
- Implantable hardware not compatible with MRI or with the study.
- MRI (done within one year of the first visit) with abnormalities other than those associated with the neurological disorder causing chronic pain.
- Inability to comply with study follow-up visits
- Previous ablative intracranial surgery for the management of the thalamic pain syndrome.
- Previously implanted with deep brain stimulation system or any previously implanted device treatment involving brain stimulation.
- Major neurological disorder other than the one that led to the chronic pain including epilepsy, neurodegenerative condition, or any history of seizure
- Requires diathermy, electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) to treat a chronic condition
- Has an implanted electronic device such as a neurostimulator, cardiac pacemaker or medication pump
- Allergies or known hypersensitivity to materials in the Activa PC+S system (i.e. titanium, polyurethane, silicone, polyetherimide, stainless steel)
- Pregnancy or lack of regular use of contraceptives. Patients who become pregnant after enrollment may be excluded from the study. Patients who become pregnant prior to the surgical implantation of the DBS systems will be excluded from the study.
- Patients may be excluded from enrollment due to a condition that, in the judgment of the PI, significantly increases risk or reduces significantly the likelihood of benefit from DBS.

5.0 Study Device(s)

Investigational

- Activa PC+S implantable pulse generator, Model 37604
- Sensing Programmer Model 8181 for Activa PC+S
- Sensing Programmer Software Model 8180 for Activa PC+S
- Intercept Patient Programmer, model 37441
- Activa PC+S lead extension model 37087
- Nexus-D (vD3) / E Systems
- Nexus-D Application Programming Interface [1] (v1.5)
- Nexus-E Activator Model 4NR005

Approved for other indications

- Medtronic Resume II paddle electrode model 3587A
- Medtronic Resume II paddle electrode model 031930
- N'Vision Clinical Programmer Model 8840
- Clinician Programmer Software Model 8870
- Patient Programmer Model 37642
- Patient Programmer Antenna Model 37092
- Lead Models 3389S / 3387S / 3391S
- External Neurostimulator 37022
- Lead extension model 37086

3.0 Study Procedure

Study Duration: The duration of this pilot study will be five years. We expect that all 10 patients will be recruited in the first 2.5 years, and data collection, stimulation and analysis will be completed at 5 years.

Patient recruitment and clinical characterization: Patients with refractory chronic neuropathic pain specific to spinal cord injury, post-stroke or phantom limb pain will be recruited from clinics specializing in chronic pain at UCSF and the San Francisco VA Medical Center. To the extent possible within our patient population, we will seek to minimize the diversity of neuropathic pain diagnoses represented across the two pain etiologies thereby optimizing opportunity for cross-patient comparative analysis.

The overall study design is summarized in **Figure 3: Overall study visit timeline. Also see Table: Protocol chart.**

The schedule of events is as follows:
PHASE 1:
Prior to surgery
1. Prior to the start of the study, an informal phone interview to schedule in-clinic evaluation will take place, (**noted as visit 1.1**). An in-person visit at the clinic will then be scheduled.

2. The research study PI(s) will obtain informed consent at the in-person visit at the clinic. During this visit, (**noted as visit 1.2**) the study team will begin establishing eligibility based on the following inclusion and exclusion criteria, **with method for establishing eligibility in parenthesis.**

i. During this visit, PI will obtain consent for medical record review by HIPAA authorization form signed by patient. Medical record review will be also done after the in-person visit.

ii. Pregnancy test and other paper-pen testing as noted below will also be conducted.

This visit will primarily serve to obtain consent for the study and HIPAA authorization, as well as discuss the study in detail and answer any questions and begin confirmation of inclusion/exclusion criteria of the patient.

iii. During visit 1.2, Inclusion / Exclusion criteria will be investigated as follows:

Inclusion:
- Patient is age ≥ 21 years **(medical record review and asking patient);**
- Clinical diagnosis of post-stroke pain (thalamic pain), Spinal Cord Injury or phantom limb pain with allodynia or dysesthesia with pinprick anesthesia or hypoesthesia on the affected hemibody or limb (anesthesia dolorosa), **(medical record review);**
- <u>For Post-Stroke Pain</u>: Stroke of ischemic etiology only. MRI done within one year of the first visit showing a lesion that involves the contralateral brainstem, thalamus or cortex. The lesion will involve cortical-subcortical areas in topography consistent with sensory thalamocortical connections. This will include patients with infarcts in the territory of the middle cerebral artery or those with cavernous malformations. A more recent MRI may be required if the patient's condition changed within the previous year. **(medical record review);**

- For Phantom limb pain: MRI done within one year not showing any contraindication to surgery such as mass, lesion, hemorrhage or other abnormality near target, **(medical record review);**
- For Spinal Cord Injury pain: MRI done within one year not showing contraindication to surgery such as mass, lesion, hemorrhage or other abnormality near target **(medical record review)**
- One year or more of medically refractory severe pain **(asking patient and medical record review);**
- Average daily pain for the past 30 days reported as >5 on a 0-10 numeric rating scale (NRS), **(asking patient and medical record review);**
- Failure to respond adequately to at least one antidepressant, one anti-seizure medication and one oral narcotic with current stable doses of medications. **(asking patient and medical record review);**
- Ability to speak / read English; **(based on conversation during informed consent and asking patient);**
- Capable of understanding and providing informed consent **(based on conversation during informed consent and asking patient);**
- Stable doses of pain medications (e.g. anticonvulsant drug, anti-depressants, and opioids etc.) **(medical record review and asking patient)**
- Women of childbearing age must be on regular use of an accepted contraceptive method(s), **(urine pregnancy test and asking patient).**

Exclusion Criteria.

- Pregnancy or breast feeding **(urine pregnancy test and asking patient).**
- Inability to speak and / or read English, **(based on conversation during informed consent and asking patient);**
- Inability to give informed consent, **(based on conversation during informed consent and asking patient);**
- Significant cognitive impairment of Dementia (MoCA<25) **(based on Montreal Cognitive Assessment paper/pen test given by research team and medical record review).**
- Aphasia severe enough to limit the consent process or communication between the investigators and the patient. Patients with mild or recovering aphasia may be considered candidates at the discretion of the PI, **(based on medical record review and conversation during informed consent).**
- Active depression (BDI > 20) or other untreated or uncontrolled psychiatric illness (active general anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or personality disorders (e.g. multiple personality disorder, borderline personality disorder, etc.) or other neuropsychiatric conditions that evaluating psychiatrist would recommend exclusion of patient after neuropsychiatric evaluation **(based on paper/pen tests of Beck Depression Inventory and Beck Anxiety Inventory scores, along with psychiatric evaluation-visit 1.3).**
- Suicide attempt </= 12 months or imminent suicide risk **(Paper/pen test of C-SSRS=Columbia Suicide Severity Rating Scale, medical record review and psychiatric evaluation, visit 1.3).**
- History of substance abuse in past 3 years, (**medical record review and psychiatric evaluation).**
- Major medical co-morbidities increasing the risk of surgery including uncontrolled hypertension, severe diabetes, major organ system failure, history of hemorrhagic stroke, need for chronic anticoagulation other than aspirin, active infection,

immunocompromised state or malignancy with < 5 years life expectancy, **(medical record review).**

- Inability to stop Coumadin or platelet anti-aggregation therapy for surgery and after surgery. Patients taking these medications will need to discuss the need/risk of continuing these medications with their physicians and the PI or study personnel may contact the treating physician(s) as well to discuss the risks of anticoagulation / antiaggregation therapy discontinuation, **(medical record review).**
- Coagulopathy. Patients will be excluded unless assessed and cleared by hematology **(medical record review).**
- Implantable hardware not compatible with MRI or with the study **(medical record review and asking patient)**.
- MRI (done within one year of the first visit) with significant abnormalities other than those associated with the neurological disorder causing chronic pain, **(medical record review).**
- Inability to comply with study follow-up visits
- Previous ablative intracranial surgery for the management of the thalamic pain syndrome **(medical record review).**.
- Previously implanted with deep brain stimulation system or any previously implanted device treatment involving brain stimulation **(medical record review).**
- Major neurological disorder other than the one that led to the chronic pain including epilepsy, or neurodegenerative condition, or any history of seizure **(medical record review).**
- Requires diathermy, electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) to treat a chronic condition, **(medical record review).**
- Has an implanted electronic device such as a neurostimulator, cardiac pacemaker or medication pump, **(medical record review).**
- Allergies or known hypersensitivity to materials in the Activa PC+S system (i.e. titanium, polyurethane, silicone, polyetherimide, stainless steel), **(medical record review).**
- Pregnancy or lack of regular use of contraceptives. Patients who become pregnant after enrollment may be excluded from the study. Patients who become pregnant prior to the surgical implantation of the DBS systems will be excluded from the study. **(urine pregnancy test and asking patient).**
- Patients may be excluded from enrollment due to a condition that, in the judgment of the PI, significantly increases risk or reduces significantly the likelihood of benefit from DBS **(medical record review).**

3. A Separate visit for psychiatric evaluation (**visit 1.3**) will evaluate patient's eligibility further for the study.

4. MRI scans (**visit 1.4**) will be obtained to establish eligibility will be done if patient does not have recent evaluation and / or scans.

After eligibility is established through the phone screen (visit 1.1), pre-study visit (1.2) and psychiatric evaluation (visit 1.3), the patient will then have a separate visit, (visit 1.4) (after additional medical record review) to obtain the following:

5. Visit 1.4 (baseline visit):

Physical examination including the following:

- Obtain patient demographics;

- Obtain major pain symptoms and site of pain;
- Obtain vital signs;
- Obtain medical history systems review;
- Obtain list of current medications taking;
- Obtain general health status;
- Obtain current physical characteristics of pain, as measured pain intensity from pain visual analog scales [];
- In the case that the visit can be coordinated with pain medication status, a pain relief VAS can also be taken after medication.
- Pen / paper forms / computerized versions for
    - clinical global impression,
    - SF-36 health survey,
    - the NIH PROMIS, tests,
    - Columbia Suicide Severity Rating Scale (C-SSRS);
    - Beck Depression Inventory (BDI);
    - Beck Anxiety Inventory (BAI);
    - Neuropathic pain questionnaire (NPQ).
- Pre-operative MRI scan will also be obtained, after the baseline visit, but prior to surgery. If needed, this can be done during the hospitalization.

6. On the day of surgery, patient will under go the following (visit 2):

- Preoperative blood work: On the day of surgery, pre-operative blood work will be obtained for for lab tests including
    - CBC,
    - BMP,
    - PT/ PTT,
    - ESR,
    - Urinalysis.
- Antibiotic medications will be given prior to surgery.
- Pre-operative MRI scan may also be obtained for surgical planning, if a recent one of adequate quality has not been obtained.
- Surgery / implant of Activa PC+S device (see below for more details) with intra-operative CT.
- Activa data collection during surgery

Surgery: DBS electrodes (Medtronic Model 3587A, 3389, 3387 or 3391 electrodes) will be inserted bilaterally or unilaterally, dependent on pain characterization (see above section 3.0), into dorsal regions of the cingulate cortex and orbital frontal cortex, specific to each patient pain characteristics and as determined at the pain neurosurgery case conference.

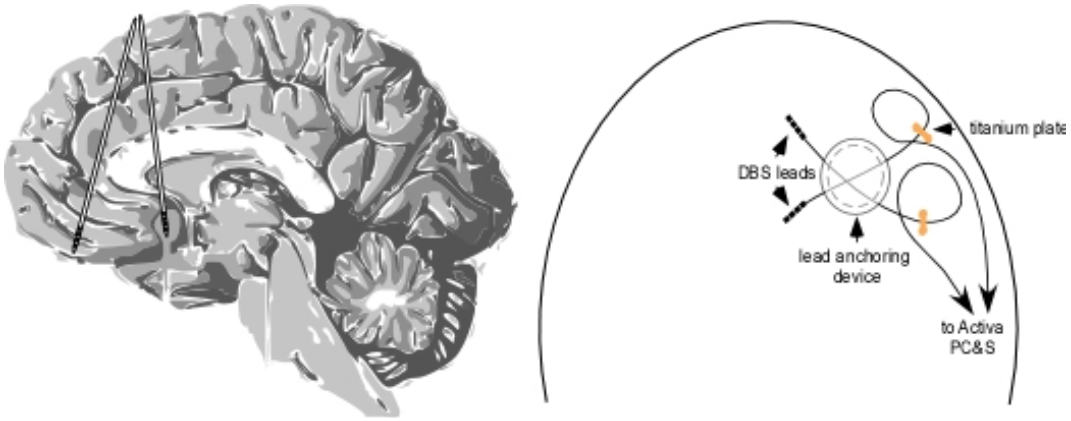


Figure 4: Schematic of unilateral implanted hardware

The leads will be advanced through two to four frontal burr holes or frontal craniotomy, dependent on implantation site and number of implantations, with correct placement confirmed by intraoperative CT [48]. Lead placements will be re-confirmed by CT at the 2-month visit, as post-operative standard of care. Stim-loc devices will be used for DBS anchoring, with a strain relief loop anterior to the site of anchoring to prevent movement or torque on the lead over time, **Figure 4: Schematic of unilateral implanted hardware**).

The free ends of the DBS leads are then placed in a subgaleal pocket, created by blunt dissection in the parietal area. After induction of general anaesthesia, the head, neck and chest are prepped and draped, and the free ends of the leads are accessed via a new 2 cm incision in the parietal area. This lead extender is tunnelled subcutaneously between the parietal incision and a 5 cm incision over the pectoralis muscle, where a pocket is bluntly dissected for the Activa system (either on one side of the chest, with one pulse generator, or both sides of the chest, with two pulse generators, dependent on patient's clinical pain presentation (see Section 3.0).

Activa Data collection sessions: During data collection we will sample two time series channels at 422 Hz or 800 Hz and also collect power spectral data at high gamma (120-150 Hz) through two separate channels allowed by PC+S. Data download is then performed non-invasively using the Medtronic model 8181 sensing programmer provided by Medtronic Inc., via a wand resting on the skin over the Activa device. At home downloads will be conducted between week 3 and month 6, with up to five data downloads per week, self-reporting on pain VAS via a web interface or text-messaging system that does not record or store any identifying patient information. At-home data collection will be optional and determined by the patient. If the patient is not able to participate in home data collection, data will only be collected in the clinic for that particular patient. It should be noted that it is NOT possible to activate stimulation with the at-home data downloads. Only recordings of the data can be sensed by the at-home sensing programmer.

7. Visit 3+: Post-operatively, prior to hospital discharge and during hospitalization:

- Clinical: follow-up physical prior to hospital discharge
- Research: Activa Data collection daily while in hospital, pain assessment for clinical characterization daily while in hospital, and C-SSRS/BDI/BAI/ NIH PROMIS /NPQ prior to hospital discharge

8. Visit 4: 10 days post implantation (+/- 3 days):

- Clinical: follow up physical and staple removal and wound check

- Research: Teach at-home patient activation of the brain recording function (see below**), Activa Data collection and C-SSRS/BDI/BAI/ NIH PROMIS /NPQ/SF-36, (including QST and baseline LFP recording), recording with painful activity, pain medication

***.Behavioral and neural states for Activa brain data collection:* For each at-home recording session, data will be collected during various conditions, four times daily, three days a week at the following times:

a. Immediately after waking up in the morning
b. 30 mins post medication use
c. afternoon between 1200 - 1400 pm
d. immediately before bedtime

Also, twice a week, patients will be asked to record during pre-identified activities that exacerbate pain (e.g. bending, climbing stairs, etc.). Patients will be asked to keep an online recording diary, in which their individual VAS scores can be updated and tabulated by the research team when recordings are made by the patient. No Identifying information will be stored or recorded through the online recording diary. Patients may also be asked to text the research team VAS scores via a cellphone when patients are recording at home.

A predictive biomarker of pain will be discovered in phase 1 from data collected with at-home and in-clinic recording sessions. This biomarker discovery will be implemented in Phase 2.

9. Visit 5: Three weeks post implantation (+/- 7 days) (research visit only):

- Activa Data collection, (including QST), recording with painful activity, pain medication:
- Baseline LFP recordings will also be taken from ~2 minutes.
- Quantitative sensory testing (QST) with the Medoc device. Using cold and heat, we will test sensory perception and pain thresholds 3 times each in the aspect of both hands (contra and ipsi lateral to pain). The device will slowly increase/ decrease temperature until the patient reports sensation (1st endpoint) and then pain (2nd endpoint) which will be recorded. Heat and cold perception and pain thresholds will be tested, with the measures of VAS for pain threshold on each trial. Three consecutive trials will be conducted in each session to establish reliability. LFP recordings will be recorded during the QST sessions with clinician initiated recording. LFP recordings will also be recorded during pre-identified painful activities or movement and after painful activity with VAS scores recorded during these times as well.
    - Patients will be asked to avoid pain medication two hours prior to their appointments. Post-testing, patients will then take medications and 2-minutes of recording will be obtained 15-minutes after pain medication is given.
- C-SSRS, BDI/BAI, Neuropathic Pain Questionnaire, NIH PROMIS Global health and physical function scales and SF-36

10. Visit 6: Two Months (+/- 10 days)

- Clinical: HEAD CT for stability
- Activa Data collection, (including QST), recording with painful activity, pain medication:

- Baseline LFP recordings will also be taken from ~2 minutes.
- C-SSRS/BDI/BAI/ NIH PROMIS /NPQ/physical function scales and SF-36

12. Visit 8-10: months 4-6, every 4 weeks:
Clinical: visits 8 and 10: History and Physical at 4 month and 6 mo.
Research: visits 8, 9, 10:

- Activa Data collection, (including QST), recording with painful activity, pain medication:
- Baseline LFP recordings will also be taken from ~2 minutes.
- Quantitative sensory testing (QST) with the Medoc device. Using cold and heat, we will test sensory perception and pain thresholds 3 times each in the aspect of both hands (contra and ipsi lateral to pain). The device will slowly increase/ decrease temperature until the patient reports sensation (1^{st} endpoint) and then pain (2^{nd} endpoint) which will be recorded. Heat and cold perception and pain thresholds will be tested, with the patient record VAS for pain threshold on each trial. Three consecutive trials will be conducted in each session to establish reliability. LFP recordings will be recorded during the QST sessions with clinician initiated recording. LFP recordings will also be recorded during pre-identified painful activities or movement and after painful activity with VAS scores recorded during these times as well.
    - Patients will be asked to avoid pain medication two hours prior to their appointments. Post-testing, patients will then take medications and 2-minutes of recording will be obtained 15-minutes after pain medication is given.
- C-SSRS/BDI/BAI/ NIH PROMIS /NPQ/physical function scales and SF-36
- We may use EEG (electroencephalography) data from a multichannel scalp electrode system to noninvasively collect brain signals that can aid in biomarker detection, using the EEGi or similar clinical system.

PHASE 2:

In the first two weeks of Phase 2, patients will be seen daily for up to two weeks to optimize DBS parameters (visits 11-24), based on biomarker discovery from Phase 1. Patients will then have closed-loop stimulation enabled for at-home stimulation, with follow-up clinic visits scheduled every 3 weeks. During this phase, patients will be monitored closely, with daily at-home phone calls and frequent in-clinic appointments. Stimulation will be enabled or disabled in an ON/OFF state with patient blinded to stimulation status to test for potential placebo / sham effects. In addition to at-home reporting (similar to Phase 1), efficacy of stimulation will be tested every three weeks in-clinic. Phase 2 will last approximately 6 months in duration, time period based on previous unpublished observations in human Parkinson's patients from our group [55] and published non-human primate observations [49], visits 11-31, if needed).

Nexus System Study: Patients who have had the Activa PC+S device implanted for approximately 4 months (Phase 1 of the clinical study) will start Phase 2 of the study, which implements the Nexus external interface. The Nexus System is capable of open-loop and closed-loop stimulation, allowing potential therapeutic applications of Activa PC+S. Patients will participate in phase 2 of the trial between 7 and 12 months post implantation, involving up to ten additional study visits, in addition to daily visits for up to the first 2 weeks of phase 2.

Stimulation will test a strategy of disruption of pain states, with optimal stimulation parameters to the orbital frontal and cingulate as determined by phase 1. Furthermore, closed-

loop stimulation will test a strategy for automated control of DBS settings with aberrant signaling in pain states triggering stimulation. To test stimulation strategies, at the start of a session in phase 2, LFP data will be collected in elevated pain states. These data will be streamed using the Nexus System in conjunction with software from the Nexus programming interface. The Nexus System provides a conduit between Activa PC+S and a computer and can transfer stimulation update commands to Activa PC+S. During the streaming procedure stimulation settings may be automatically, iteratively, adjusted based on markers of oscillatory activity such as cortical phase-amplitude coupling (PAC) or beta band power. These adjustments will always remain within allowable settings pre-programmed by a clinician using standard procedures (i.e. using the Medtronic 8840 programmer).

Phase 2 will test the effectiveness of closed-loop stimulation in comparison to no-stimulation. Daily visits will take place for the first 2 weeks of phase 2, and regular clinic visits occurring every three weeks during Phase 2 (~ 6 months in duration).

Stimulation states for Activa PC+S brain data collection: In phase 1, the optimal times of day that patients are most likely in a pain state will be assessed and used to schedule appointments in the outpatient clinic for phase 2 (i.e., we will schedule phase 2 recording and stimulation sessions for each patient to coincide with optimal time of pain states, as determined by patterns of maximum and predictable pain states from phase 1). In Phase 2, for the first recording session that includes a DBS-on condition, (after the initial up to 2 week period of optimizing stimulation parameters), the following data will be recorded:

1) VAS pain, VAS unpleasantness, C-SSRS, BDI/BAI, Neuropathic Pain Questionnaire, NIH PROMIS Global health and physical function scales and SF-36
2) Baseline LFP
3) Stimulation off + QST (no pain medication)
4) Stimulation on + QST
5) Wash-out, stimulation off period
6) LFP recording after painful activity
7) Recording after pain medication
8) EEG activity

Visits are as follows:

13. Visit 11-24: Every day for 2 weeks, stimulation optimizing:

- Clinical only: Daily visits 11-24 DBS programming initial and revisits if needed. Full history and physical exams to document changes that occur during closed loop stimulation.
- Research: C-SSRS, BDI/BAI visits 11, 18 and 24.

14. Visits 25-31: every 3 weeks for closed loop / placebo randomization:

- Clinical: visit 28 only; History and Physical for stability
- Research: visits 25-31: Activa Data collection + QST:
- Quantitative sensory testing (QST) with the Medoc device. Using cold and heat, we will test sensory perception and pain thresholds 3 times each in the aspect of both hands (contra and ipsi lateral to pain). The device will slowly increase/ decrease temperature until the patient reports sensation (1st endpoint) and then pain (2nd endpoint) which will be recorded. Heat and cold perception and pain thresholds will be tested, with the patient record VAS for pain threshold on each trial. Three consecutive trials will be conducted in each session to establish reliability. LFP recordings will be recorded during the QST sessions with clinician initiated recording. LFP recordings will also be recorded during pre-identified painful activities or

movement and after painful activity with VAS scores recorded during these times as well.
- Patients will be asked to avoid pain medication two hours prior to their appointments. Post-testing, patients will then take medications and 2-minutes of recording will be obtained 15-minutes after pain medication is given.
- Baseline LFP recordings will also be taken from ~2 minutes.
- Stimulation off + QST (no pain medication)
- Stimulation on + QST
- Wash-out, stimulation off period
- LFP recording after painful activity
- Recording after pain medication
- C-SSRS/BDI/BAI/ NIH PROMIS /NPQ/physical function scales and SF-36

Phase 2 will last approximately 6 months in duration, time period based on previous unpublished observations in human Parkinson's patients from our group [143] and published non-human primate observations [58], visits 11-34, if needed)

Phase 2 will test the effectiveness of closed-loop stimulation in comparison to no-stimulation.

In phase 3, the effectiveness of closed-loop stimulation will be tested in comparison to open-loop stimulation settings.

Phase 3
In phase 3, patients will continue with at-home stimulation with either personalized closed-loop or traditional open-loop stimulation strategies their implanted system. Patients will be blinded to the stimulation strategy in which they are assigned. Assignment of open-loop or closed-loop will be randomized and occur in 6-week time periods, with each patient serving as his or her control as to which stimulation treatment is more effective.

During this phase, patients will be monitored closely, with daily at-home phone calls and frequent in-clinic appointments. This phase of the study will last approximately 1 year (time line based on previous published reports [3, 11, 202, 85, 94], with in-clinic appointments occurring approximately every 6 weeks. Patients may also participate in at-home reporting (similar to Phase 1 and Phase 2).

In-clinic appointments will consist of the following:
1) VAS pain, VAS unpleasantness, C-SSRS, BDI/BAI, Neuropathic Pain Questionnaire, NIH PROMIS Global health and physical function scales, and SF-36
2) Baseline LFP
3) Stimulation off + QST (no pain medication)
4) Stimulation on + QST
5) Wash-out, stimulation off period
6) LFP recording after painful activity
7) Recording after pain medication
8) Closed-loop DBS being turned to open-loop stimulation setting, or previous open-loop stimulation being turned to closed-loop DBS setting, randomized
9) EEG activity

15. Visit 32-41 ++: Months 13-24: Every 6 weeks, +/- 10 days); Assignment to open-loop or closed loop, blinded randomization every 6 weeks.

Clinical: visit 32, 36, 39 and final visit of study: Health status and physical by physician;

Research: visits 32-41++: Activa Data collection and VAS scores before and during stimulation, (including QST), recording with painful activity, pain medication.

- Research: visits 32-41++: Activa Data collection + QST:
- Quantitative sensory testing (QST) with the Medoc device. Using cold and heat, we will test sensory perception and pain thresholds 3 times each in the aspect of both hands (contra and ipsi lateral to pain). The device will slowly increase/ decrease temperature until the patient reports sensation (1st endpoint) and then pain (2nd endpoint) which will be recorded. Heat and cold perception and pain thresholds will be tested, with the patient record VAS for pain threshold on each trial. Three consecutive trials will be conducted in each session to establish reliability. LFP recordings will be recorded during the QST sessions with clinician initiated recording. LFP recordings will also be recorded during pre-identified painful activities or movement and after painful activity with VAS scores recorded during these times as well.
- Patients will be asked to avoid pain medication two hours prior to their appointments. Post-testing, patients will then take medications and 2-minutes of recording will be obtained 15-minutes after pain medication is given.
- Baseline LFP recordings will also be taken from ~2 minutes.
- Stimulation off + QST (no pain medication)
- Stimulation on + QST
- Wash-out, stimulation off period
- LFP recording after painful activity
- Recording after pain medication
- C-SSRS/BDI/BAI/ NIH PROMIS /NPQ/physical function scales and SF-36

++Patients may have the option to continue at-home stimulation, in which additional visits, every 6 weeks, would be required for follow-up.

16. Final Research visit: Post-intervention Neuropsychological / Behavioral testing. Various pen/paper and computerized neuropsychological tests will be given. Evaluation by study researchers will also taken place.

Phase 3 will inform the research team as to whether open-loop or closed-loop stimulation is most effective on a patient-by-patient basis.

Table: Protocol Chart

Study visit	Time	Activities	Phases
1.1	Within 90 days prior to surgery	**Clinical: None** **Research: Phone screen**	**Phase 1:** 0 to 6 months; 8-10 visits
1.2 Pre-study visit		**Research:** Informed Consent; HIPPA Authorization for medical record review; Establish eligibility through inclusion / exclusion criteria Inclusion Criteria: patient interview (including numeric rating scale of pain for past 30 days), medical record review, urine pregnancy test Exclusion Criteria: Montreal Cognitive Assessment (MoCa), Beck Depression Inventory and Beck Anxiety Inventory ,	
1.3		**Clinical: Psych evaluation (also part of Eligibility);** **Research: Columbia Suicide Severity Rating Scale**	
1.4 Baseline		**Clinical:** History and Physical include current meds, vitals, general health, physical characteristics of pain, as measured by VAS; pain relief from meds as measured by VAS, Pre-operative MRI will also be obtained, after the baseline visit, but prior to surgery. If needed, this can be done during the hospitalization. **Research:** clinical global impression, SF-36, C-SSRS/BAI/ NIH PROMIS /NPQ	
2	Day of surgery	**Clinical:** possibly pre-op MRI for surgical planning if one of adqeuate quality has not been obtained preoperative labs (CBC, BMP, PT/PTT, ESR and urinalysis) antibiotics (prior to surgery) Implant surgery, CT Head **Research:** Activa Data collection (intraoperatively and daily while in hospital)	
3	Post-operatively, prior to hospital discharge, and during hospitalization	**Clinical: follow-up physical prior to discharge** **Research:** Activa Data collection daily, pain assessment daily for clinical characterization, and C-SSRS/BDI/BAI/ NIH PROMIS /NPQ prior to discharge	
4	10 days post implantation (+/- 3 days)	**Clinical:** **follow up physical** and staple removal and wound check **Research:** **Teach at-home monitoring,** Activa Data collection and C-SSRS/BDI/BAI/ NIH PROMIS /NPQ, (including QST+ baseline LFP recording), recording with painful activity, pain medication	
5	Three weeks post implantation (+/- 7 days) Visit for research only	**Clinical: none** **Research visit only: visit 5** Activa Data collection and C-SSRS/BDI/BAI/ NIH PROMIS /NPQ/SF-36, (including QST), recording with painful activity, pain medication	
6	Two Months (+/- 10 days)	**Clinical:** HEAD CT for stability **Research:** Activa Data collection and C-SSRS/BDI/BAI/ NIH PROMIS /NPQ/SF-36, (including QST+baseline LFP recording), recording with painful activity, pain medication	
7	Three Months (+/- 10 days);	**Clinical: none** **Research visit only:** Activa Data collection and C-SSRS/BDI/BAI/ NIH PROMIS /NPQ/SF-36, (including QST+baseline LFP recording), recording with painful activity, pain medication	
8-10	Every 4 weeks	**Clinical: visits 8 and 10:** History and Physical at 4 month and 6 mo. **Research: visits 8, 9, 10:** Activa Data collection and C-SSRS/BDI/BAI/ NIH PROMIS /NPQ, SF-36 (including QST+baseline LFP recording), recording with painful activity, pain medication	
11-24	Every day for 2 weeks, stimulation optimizing (START PHASE 2)	**Clinical only: visits 11-24** DBS programming initial and revisits if needed.; **Research:** 11 and 24 visit: C-SSRS/BDI/BAI	**Phase 2:** Months 7-12; Daily visits for 2 weeks followed by 7 study visits
25-31	every 3 weeks for closed loop randomization	**Clinical: visit 28 only;** History and Physical for stability **Research: visits 25-31;** Activa Data collection and VAS scores before and during stimulation, including QST+baseline LFP recording, recording with painful activity, pain medication. C-SSRS/BDI/BAI/ NIH PROMIS /NPQ, SF-36. DBS on/ off	
32-41	(Every 6 weeks, +/- 10 days), Months 13-24 (PHASE 3)	**Clinical: visit 32 and 36 and final visit of study:** H&P for stability **Research: visits 32-41:** Activa Data collection and VAS scores before and during stimulation, (including QST+baseline LFP recording), recording with painful activity, pain medication; (including QST), recording with painful activity, pain medication. C-SSRS/BDI/BAI/ NIH PROMIS /NPQ, SF-36. DBS open vs closed **Final Research visit:** Post-intervention Neuropsychological / Behavioral testing	**Phase 3:** Months 13-24; visit every 6 weeks, 8-10 visits

*Abbreviation: C-SSRS=Columbia Suicide Severity Rating Scale; BDI=Beck Depression Inventory; BAI=Beck Anxiety Inventory.

Progression of phases: We anticipate approximately 6 months for phase 1, a time period based on previous studies [2, 85]. As phase 2 may provide a potential for therapeutic relief of pain symptoms, if patients' pain signatures are reliably detected in a shorter time period in phase 1, the patient may opt to proceed to phase 2 at an earlier time point (i.e. fewer sessions for phase 1). If data of sufficiently high quality is collected before the 6 month phase period ends in Phase 2, depending on pain relief symptoms, the research team may accelerate phase 2 to phase 3 before the 6-month period ends to ensure rapid positive clinical outcomes (in which longer pain relief may occur).

In certain patients who do not experience a sufficiently wide range of pain fluctuation scores (ie. Pain ranges always from 8-9 /10) , it may be difficult to create a predictive model of pain from neural data during phase 1. In these cases, we may opt to proceed to phase 2 at an earlier time point, as soon as 6 weeks post-implantation. Using potentially therapeutic stimulation of ACC or OFC to decrease pain scores at the start of phase 2, we can then aim to calculate biomarkers of pain relief and elevated pain states at the start of phase 2 during stimulation optimization. Additionally, if in phase 1 we anticipate difficulty in successfully collecting biomarker information for any reason, we may opt to progress to phase 2 at an earlier time point to support a positive clinical outcome for the patient.

Conclusion of study: Formal data collection will be completed at 24 months post implantation. However, it is expected that patients will be followed for life in our clinic, as is the case for most patients implanted with DBS devices. At the end of the clinical trial, in consultation with patients' regular pain management teams, patients may be offered a potential therapeutic stimulation strategy (either open-loop or closed-loop), dependent on his or her pain alleviation from the clinical trial period. Patients will have the option to 1) continue active stimulation at the current setting with current device implantation, 2) continue stimulation but searching for a new setting, 3) discontinue stimulation (turning the device off) or 4) have the device removed. If patients opt to continue at-home active DBS after formal data collection has been completed, follow-up appointments will occur every 6 weeks.

Patient activation of the brain recording function: All data collection in the formal study visits described above will be initiated by the study staff. In addition to these data collections, the patient will be given the Intercept Patient Programmer, model 37441, allowing triggered brain data recording in their own home at specified times (see above). Patient will be instructed how to collect and download data at home. If the patient is not comfortable downloading the data at home, a family member or friend can also be taught how to use the device for download, or with the patient's permission, arrangements can be made for the study staff to visit the patient's home for data downloads. Study staff may also arrange with patients to visit their homes to help with initiating data collection. Such visits will ensure that data collection is initiated correctly, and by completing downloading at home, will reduce time spent during formal study visits to the clinic. The intercept patient programmer does not enable stimulation of the electrodes; it only enables recordings of the data and is thus safe for patients to use at-home after initial training with research staff.

Nexus System Study: Patients who have had the Activa PC+S device implanted for approximately 4 months (Phase 1 of the clinical study) will start Phase 2 of the study, which implements the Nexus external interface. The Nexus System is capable of open-loop and closed-loop stimulation, allowing potential therapeutic applications of Activa PC+S. Patients will participate in phase 2 of the trial between 7 and 12 months post implantation, involving up to ten additional study visits.

Stimulation will test a strategy of disruption of pain states, with optimal stimulation parameters to the orbital frontal and cingulate as determined by phase 1. Furthermore, closed-loop stimulation will test a strategy for automated control of DBS settings with aberrant signaling in pain states triggering stimulation. To test stimulation strategies, at the start of a session in phase 2, LFP data will be collected in elevated pain states. These data will be streamed using the Nexus System in conjunction with software from the Nexus programming interface. The Nexus System provides a conduit between Activa PC+S and a computer and can transfer stimulation update commands to Activa PC+S. During the streaming procedure stimulation settings may be automatically, iteratively, adjusted based on markers of oscillatory activity such as cortical phase-amplitude coupling (PAC) or beta band power. These adjustments will always remain within allowable settings pre-programmed by a clinician using standard procedures (i.e. using the Medtronic 8840 programmer).

Phase 2 will test the effectiveness of closed-loop stimulation in comparison to no-stimulation. Daily visits will take place for the first 2 weeks of phase 2, and regular clinic visits occurring every three weeks during Phase 2 (~ 6 months in duration).

In phase 3 (year 2 of the study), the effectiveness of closed-loop stimulation will be tested in comparison to open-loop stimulation settings. Patients will be blinded to the stimulation strategy in which they are assigned. Assignment of open-loop or closed-loop will be randomized and occur in 6-week time periods, with each patient serving as his or her control as to which stimulation treatment is more effective.

During this phase, patients will be monitored closely, with frequent at-home phone calls and in-clinic appointments. This phase of the study will last approximately 1 year (time line based on previous published reports [2, 85, 94], with in-clinic appointments occurring approximately every 6 weeks.

For the first two weeks of Phase 3, medical staff or researchers will contact patients on a daily basis to examine any changes in mood or pain symptoms. Clinic visits will also be scheduled every 6 weeks for 1 year, to examine pain and mood symptoms and routine follow-up care.

Conclusion of study: Formal data collection will be completed at 24 months post implantation. However, it is expected that patients will be followed for life in our clinic, as is the case for most patients implanted with DBS devices. At the end of the clinical trial, in consultation with patients' regular pain management teams, patients may be offered a potential therapeutic stimulation strategy (either open-loop or closed-loop), dependent on his or her pain alleviation from the clinical trial period. Patients will have the option to 1) continue active stimulation at the current setting with current device implantation, 2) continue stimulation but searching for a new setting, 3) discontinue stimulation (turning the device off) or 4) have the device removed. If patients opt to continue at-home active DBS after formal data collection has been completed, follow-up appointments will occur every 6 weeks.

The end of battery life for Activa PC+S is expected to occur 2-4 years after placement, depending on the chronic therapeutic stimulation parameters (similar to the sister device Activa PC that does not have a sensing function). The lead extender connecting the DBS leads to the pulse generator should not require replacement. When battery end of life occurs, it is expected that the Activa PC+S system will be removed, via the original chest incision, or replaced, dependent on further obtained approval based on the data collected in the present study and consultation with the regular pain management team.

4.0 Clinical Measurements

Primary

Clinical ratings of pain will be measured by visual analog scales for pain as well as unpleasantness of pain sensation (i.e. “how much pain are you in right now?” and “how much is the pain bothering you right now?”). Patient reports of sensory and pain detection using the Quantitative sensory testing (QST) with the Medoc device will also be used, with and without stimulation.

Physiological measurements related to neural oscillatory activity during various triggered neural recordings with various pain states, activity states, medication states, etc. (~14 recordings per week at home, ~6-8 recordings per in-clinic visit,) will include: wide spectrum power-spectral analysis as well as using specific frequency domain for mean log power (i.e. in the delta, theta, alpha, beta, gamma bands), pain-related changes in broad spectrum power density, and coupling between the phase of low frequency rhythms and broadband gamma amplitude (phase-amplitude coupling, abbreviated PAC) [145-147].

Clinical measures and physiological measurements will be collected and recorded by members of the research and clinical team, as well as from at-home data collection sessions.

Secondary

Measures from Neuropathic Pain Questionnaire, Beck Depression and Anxiety, NIH PROMIS Global health and physical function scales and SF-36 will also be compared from pre-intervention to post Phase 1, phase 2 and phase 3 time points.

5.0 Data Management

All physiological data will be stored in password-protected computers in the PI's laboratory that is always locked with a touchpad keyless entry system. Data will be backed up on UCSF's HIPPA-compliant server. In publications or presentations of the data, data will be grouped by case number in chronological order with no name identification. All DBS patients at our center routinely undergo videotaping and sign a separate consent to be videotaped. When presenting videotape data at scientific conferences, we will utilize only videos from patients who have consented to have their videos shown. De-identified electrophysiological data may be shared with other researchers at other institutions.

Clinical data (baseline and follow up rating scales) will be entered into a customized, password-protected encrypted web-based database (LAVA). This resides on a server at UCSF and is managed by the Department of Neurology, with backup support by the information technology service at UCSF. The database can be accessed by a licensed user from a secure Internet server at UCSF but is protected by firewalls from networks outside of our institution.

Any on-line or text messaging data collected will not include personal identifiers.

6.0 Statistical Methods and Data Analysis

Ratings of pain will be measured by visual analog scales for pain as well as unpleasantness of pain sensation (i.e. "how much pain are you in right now?" and "how much is the pain bothering you right now?"). Patient reports of sensory and pain detection using the Quantitative sensory testing (QST) with the Medoc device will also be used, with and without stimulation.

In Phase 2, patients will serve as their own controls in a single-blinded phase (6-months in duration) in which placebo versus active open-loop stimulation is used. During this 6-month period, four sham and four active stimulation periods will occur in a random, blinded assignment. During the 8 in-clinic visits, the threshold for sensory and pain detection with the Medoc device will be used and scores will be compared for each patient during sham versus active stimulation periods in one-sample, two-tailed t-test. The 10 patients' sham versus stimulation scores will also be used in group analysis to test the effects of open-loop and closed-loop stimulation.

In Phase 2, the visual analog scale scores recorded during the at-home recording sessions for various activities will be compared for each patient [(see Figure 3; 168 scores for sham sessions and 168 scores for active stimulation sessions, per patient); (i.e. 3 times per week for 4 activities and 2 times per week for at least 1 painful activity, for at least 14 VAS scores per week; 24 weeks total with 3 weeks per session-sham or stimulation, 8 sessions total, 4 sham sessions and 4 stimulation sessions)].

Multiple regression analysis of all patients will also be used to test for effects of stimulation on various activities, time of day, stimulation effects over time in trial and potential differences in stimulation effects on pain etiologies (i.e. spinal cord injury versus phantom limb versus post-stroke).

Phase 1 (no-intervention) VAS scores will be compared to Phase 2 (sham controlled and active stimulation) VAS scores.

In Phase 3, patients will serve as their own controls in a single-blinded phase (12-months in duration) in which closed-loop versus active open-loop stimulation is used. During this 12-month period, ~four sham and ~four active stimulation periods will occur in a random, blinded assignment. During the ~8-9 in-clinic visits, the threshold for sensory and pain detection with the Medoc device will be used and scores will be compared for each patient during sham versus active stimulation periods in one-sample, two-tailed t-test. The 10 patients' sham versus stimulation scores will also be used in group analysis to test the effects of open-loop and closed-loop stimulation.

In Phase 3, the visual analog scale scores recorded during the at-home recording sessions for various activities will be compared for each patient [(see Figure 3; ~364 scores for sham sessions and ~364 scores for active stimulation sessions, per patient); (i.e. ~3 times per week for 4 activities and 2 times per week for at least 1 painful activity, for at least ~14 VAS scores per week; ~52 weeks total with 6 weeks per session-sham or stimulation, ~8 sessions total, 4 sham sessions and 4 stimulation sessions)].

Multiple regression analysis of all patients will also be used to test for effects of stimulation on various activities, time of day, stimulation effects over time in trial and potential differences in stimulation effects on pain etiologies (i.e. spinal cord injury versus phantom limb versus post-stroke).

Phase 1 (no-intervention) and Phase 2 (sham controlled and open-loop stimulation) VAS scores will be compared to Phase 3 (open-loop stimulation and closed-loop) VAS scores.

LFP data will be analyzed using wide spectrum power-spectral analysis as well as using specific frequency domain for mean log power (i.e. in the delta, theta, alpha, beta, gamma bands). We will also examine coherence and cross-frequency coupling between the channels [145-147]. Using a repeated measures ANOVA statistical analysis, summary statistics for power in relevant frequency bands, pain-related power changes, and indices of phase-amplitude coupling will be compared at different time points, different DBS conditions (on and off), possible medication states (on and off) and different pain states. Although the sample size is small, we will assess the correlation between pain and non-pain states with brain physiology measures, and clinical instruments used to measure pain relief produced by DBS. Additionally, bootstrapping statistical applications (i.e. a Monte Carlo algorithm) and general linear mixed models can be utilized to investigate potential statistical effects, given the small sample size.

Neural activity will be compared during pain states, activity states, medication states, etc. for Phase 1 (no-intervention), as well as Phase 2 (sham controlled and open-loop stimulation) and Phase 3 (open-loop stimulation and closed-loop stimulation).

Sample size calculation: This is a pilot study consisting of existing chronic brain recording technology. The goals are to provide pain relief strategies using the Activa PC+S neural interface, as well as assess feasibility and to collect data that will be used to inform treatment plans using DBS mechanisms. Thus, there is no formal sample size calculation. However, the study is designed such that patients will serve as their own controls in a blinded, placebo versus active open-loop stimulation design, with multiple periods of placebo versus active stimulation. Patients will also serve as their own controls in open-loop versus closed-loop stimulation, in a randomly assigned, blinded, multiple 6-week time periods of open-loop versus closed-loop stimulation. At-home recording sessions will also be utilized to increase the number of testing samples per patient over the trial. In this manner, the statistical power is increased to show treatment efficacy in either of these phases.

Criteria for study success that would justify a larger subsequent trial: This study will be considered to justify a larger subsequent trial if we can demonstrate that:

1) Chronic LFP recordings are of adequate quality to assess the LFP signatures of elevated pain.
2) No permanent serious adverse events occur (such as trauma with long-term motor deficit).
3) Using the Nexus System, therapeutic benefit from stimulation can be demonstrated (i.e. cessation of a pain episode or decreased pain symptoms).

7.0 Regulatory Requirements

Prior to the start of the study, the following documents will be collected and filed:

- Signed protocol signature page
- Curriculum vitae of the PIs and Sub-investigators, updated within 2 years
- Current medical licenses for the PIs and all Sub-investigators
- Financial disclosure form signed by the PIs and all Sub-investigators listed on the
- Copy of the IRB approval letter for the study and the IRB Membership List
- Investigator Agreement

Investigators Obligations

Drs. Chang and Shirvalkar will be responsible for ensuring that all study site personnel, adhere to all FDA regulations and guidelines regarding clinical trials, including guidelines for GCP (including the archiving of essential documents), both during and after study completion. Additionally, they will be responsible for the subject's compliance to the study protocol.

All information obtained during the conduct of the study with respect to the patients' state of health will be regarded as confidential. This is detailed in the written information provided to the patient. An agreement for disclosure of any such information will be obtained in writing and will be signed by the patient.

Informed Consent

The investigators will obtain and document informed consent for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures.

Institutional Review Board

This protocol and relevant supporting data were submitted and approved by the UCSF IRB (UCSF, Human Research Protection Program, 3333 California Street, Suite 315, San Francisco, CA, 94118, FWA#00000068; IRB Registration 00000229, Lisa Denney, HRRP Director, please see **Appendix G**). Amendments to the protocol will also be submitted to the IRB prior to implementation of the change. The PI is responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The IRB must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PI. The PI must notify the IRB in writing of any SAE or any unexpected AE according to ICH guidelines.

Data safety monitory board (DSMB) and safety monitoring plan

Treatment emergent adverse events that are assessed by the principal investigators as possibly, probably, or definitely related to surgical implantation or chronic cortical recording AND are unexpected or meet seriousness criteria (death, immediately life threatening, hospitalization >24 hours, persistent or significant disability, or significant intervention required to prevent one of the previously-stated outcomes) will be recorded and reported to the IRB, device manufacturer and the FDA via the MedWatch online voluntary reporting form within 10 working days of the study team's knowledge of the event.

All such events will also be reported to the data safety monitor board (DSMB), led by Dr. Line Jacques, a neurosurgeon at our home institution, who does not have direct involvement in this study but who has expertise in implantable devices, pain management and neurosurgery. The DSMB will meet regularly to review data related to the clinical trial, provide guidance and feedback, and review any adverse event reports. Treatment-related adverse events assessed as definitely, probably, or possibly related to study procedures and either serious or unexpected, noted by any study personnel will be reported within 10 working days of their knowledge of the event to the DSMB. The DSMB will then advise the PI on potential changes in procedures to improve safety. The safety endpoint will consist of all adverse events.

Throughout the clinical trial, should a serious adverse event occur that is assessed to be surgery or stimulation-related, or related to the presence of the DBS leads, such as focal seizure or motor weakness congruent with device localization or infection, in discussion with the patient and DSMB, a decision will be made regarding the possibility of lead removal and the study being halted for the patient. Removal will be accomplished by re-opening the original incisions and grasping the lead at or just posterior to the burr hole originally used for placement.

Furthermore, if there is a serious surgery or stimulation-related adverse event, or if the patient reports greater than 25% increased pain (post-surgery recovery period compared to pre-surgery) or onset of suicidality, the study will be halted for the patient.

If two patients meet one or more of these criteria (i. serious surgery or stimulation-related adverse event, ii. greater than 25% increase pain, or iii. onset of suicidality), the study will be halted until information is reviewed by the DSMB and FDA.

Release of results on pre-specified outcomes

All outcomes that are negative or positive arising in the first 10 months of the study will be reported in peer-reviewed published journals within 1 year of surgical implantation. Continued published reports will occur as additional patients undergo surgery and treatment, with outcomes being reported within 1 year of their appearance. Release of negative outcomes will be within less than 1 year if the study is terminated early.

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