Study Title	Convection Enhanced Delivery of Autologous Cerebral Spinal Fluid Improves MRI Visualizations of Basal Ganglion Nuclei During Deep Brain Stimulation Surgery
Indication Studied	DBS (globus pallidum or subthalamus) for treatment of medication-refractory Parkinson's disease
Protocol Version	5.0
Development Phase of Study	Feasibility
GCP Statement	This study is to be performed in full compliance with acceptable Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality	This document is confidential and the property of the University of Virginia. No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorization from the study sponsor.

Principal Investigator

Dr. William Jeffrey Elias
Department of Neurological Surgery
University of Virginia
Box 800212
Charlottesville, VA 22908
(434) 924-0451 (434) 982-3806 fax

SIGNATURE PAGE

INVESTIGATOR'S AGREEMENT

I confirm that I have read this protocol and I agree to conduct the study as outlined herein. I agree to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices as outlined in ICH E6 and the applicable laws and regulations.

Investigator:	Signature	Date
	Name	

SYNOPSIS

Title of Study: Convection Enhanced Delivery of Autologous Cerebral Spinal Fluid Improves MRI Visualizations of Basal Ganglion Nuclei During Deep Brain Stimulation Surgery	
Investigator(s): W. Jeffrey Elias, MD	
Study center(s): University of Virginia Medical Center	
Phase of study: Feasibility	**Planned Study Initiation:** January 2018

Objectives: The proposed study will evaluate safety foremost but also the distribution and initial effectiveness of infusion-enhanced, MRI-guided DBS for patients with medication-refractory, Parkinson's disease.

Primary:

- To evaluate the incidence and severity of adverse events (AEs) associated with convection enhanced delivery of autologous CSF into the internal segment of the globus pallidus or subthalamic nucleus in patients with advanced PD who are undergoing DBS surgery.

Secondary:

- To determine the volume of distribution (Vd) relative to the volume of infusion (Vi) for a convective infusion of autologous CSF into a deep brain nuclear region in humans
- To determine the level of effectiveness or symptom response of infusion-enhanced, MRI-guided DBS.

Methodology: Open-label, single-arm, quantitative study

Number of subjects (planned): 4

Diagnosis and main criteria for inclusion: Patients with Parkinson's disease and medically-refractory motor symptoms, who are already planned for MRI-guided DBS electrodes under general anesthesia.

Investigational intervention: Unilateral infusion of 0.5 ml autologous CSF before DBS electrode insertion with MRI monitoring.

Other study intervention(s): None

Criteria for evaluation (i.e. endpoints):

Efficacy:

The primary efficacy assessment will be measured with the unmedicated UPDRS, motor subsection (part III) at 6 months in comparison to baseline. Additional efficacy endpoints will include standard, validated assessments of PD before and after DBS. Standard clinical measures of PD will be obtained as per usual clinical protocol at pretreatment baseline and 6 months postoperatively.

Safety:

Safety will be assessed by incidence and severity of AEs, changes in physical examinations, neurological exams and the number of discontinuations due to AEs.

Distribution:

Distribution will be assessed using MRI imaging to calculate the volume of distribution of autologous CSF into the basal ganglia in relation to the volume infused.

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
ACUC	Animal Care and Use Committee
AE	Adverse Event
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CED	Convection-Enhanced Delivery
CFR	Code Of Federal Regulations
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DBS	Deep Brain Stimulation
ECG	Electrocardiogram
FDA	Food And Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GPe	External Globus Pallidum
GPi	Internal Globus Pallidum
HCG	Beta-Human Chorionic Gonadotropin
HR	Heart Rate
h	Hour
I/E	Inclusion Exclusion Criteria
ICF	Informed Consent Form
ICH	International Conference On Harmonization
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic Resonance Imaging
min	Minute
PD	Parkinson's Disease
PK	Pharmacokinetic
RR	Respiratory Rate
SAE	Serious Adverse Event
STN	Subthalamic Nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
UVA	University of Virginia
Vd	Volume of distribution
Vi	Volume of infusion
WOCBP	Women of Childbearing Potential

2. BACKGROUND AND RATIONALE

2.1. Study Synopsis

This will be a small feasibility study investigating the safety and feasibility of infusion-enhanced, MRI-guided DBS electrode placement. We intend to enroll four (4) patients, with Parkinson's disease and medically-refractory motor symptoms, who are already planned for MRI-guided DBS electrodes under general anesthesia. Only a single side (nondominant) will be investigated with the research infusion when bilateral DBS electrodes are planned.

2.2. Disease Background

MRI-guided surgery was initially developed in the 1990s for a more precise brain biopsy.[1,7] Recently, image-guided DBS has been proposed as an alternative to traditional electrophysiologically-guided DBS for medically-refractory Parkinson's disease.[2,11,13-16,18] MRI-guided DBS can be performed under general anesthesia to avoid the discomfort of awake surgery and the need for prolonged unmedicated states. Clinical outcomes note improved off medication UPDRS motor scores by 60% and 49%, respectively which compares similarly to a recent meta-analysis of 34 studies estimating 52% in PD with STN DBS.[9]

True image-guided surgery adjusts to brain shifting during the procedure and the inherent registration errors that can be associated with image fusion techniques.[4,8] Contemporary MRI continues to improve so that small stereotactic targets, that previously required intraoperative confirmation of their location with recordings or clinical testing, can now be directly visualized, however there is still room for improvement. McClelland et. al. analyzed electrodes placed using frame-based stereotaxy and microelectrode recording guidance, and found that 40 of 52 electrodes required re-positioning based on electrophysiologic localization.[10] Unfortunately one can't determine whether this is from frame placement error, image fusion, MRI distortion, or stereotactic positioning error.

The assessment of DBS electrode placement relative to a selected target location in stereotactic space is relatively simple, requiring only postoperative imaging to compare with the preoperative plan. Real-time image-guided DBS placement has only recently been realized with compatible skull-mounted frames and high-field MRI. Radial vector error during DBS for PD has been measured at 1.2 ± 0.65 and 0.8 ± 0.4 mm.[12,16] CT has also been used as a modality to guide asleep DBS surgeries although it is primarily used for image registration and confirmation of the placement as opposed to true image guided, localization during the procedure. Burchiel et al reported similar accuracies, but clinical outcomes are not yet available.[2]

Even with highly precise MRI-guided placement, the need for occasional electrode repositioning exists.[16] This work was pursued on the assumption that improved resolution of these deep brain structures will aid stereotactic targeting, ultimately improving patient outcomes. We are interested to investigate if the combined use of intraoperative MRI-guided electrode placement, with improved target visualization from infusions, will improve patient outcomes as determined from UPDRS. The potential applicability of this technique to humans has many issues. First and foremost, the risk/benefit ratio must be favorable to ultimately consider infusion-enhanced, MRI-guided surgery as a valid surgical option. We perceive the addition of a small volume infusion (<0.5 ml) of autologous CSF to be associated with low morbidity. The increased risk of micro-catheter insertion should be similar or less than the current electrophysiological mapping process that requires multiple, sharp microelectrode penetrations. The safest infusate to test intuitively would be autologous CSF which is easily and safely obtained by lumbar puncture from patients who are already under general anesthesia.

Finally, the preclinical study described a proof-of-concept technique that mainly relies on the improved visualization of structures like the STN from T2 signal manipulation in the laboratory and clinic. Other structures like the internal segment of the globus pallidum or the ventral intermediate nucleus of the thalamus are better visualized with other MR sequences like inversion recovery or susceptibility-weighted images, respectively. In the future, we envision that infusion-enhanced MR imaging would be tailored to the desired brain target with target-specific sequences and infusates. For example, a choline-specific infusate could be designed to visualize the basal nucleus of Meynert if a neuroprotective or regenerative intervention were available for Alzheimer's disease. Imaging of all modalities will continue to improve with technology, but tailored intracerebral infusions may serve as an adjunct for improved visualization, not as a replacement for current imaging.

2.3. Case Study

A 59-year-old retired psychologist with Parkinsons disease presented for consideration of deep brain stimulation surgery. He underwent successful surgery consisting of bilateral subthalamic nucleus DBS with micro-electrode mapping and a staged pulse generator implantation. Unfortunately, he developed a pseudomonas infection involving the pulse generator, which required explantation of the pulse generator and the distal portion of the lead extensions. Despite ciprofloxacin therapy, he presented again two months later with evidence of infection at the cranial incision. Cerebral MRI with gadolinium revealed no intracranial abscess, however, there was hyperintense signal on T2 weighted images around the right DBS electrode tract to the subthalamus (Figure 1). The remainder of the DBS system was explanted, and the infection was cleared after several weeks of intravenous aztreonam therapy. A second bilateral subthalamic DBS system was eventually re-implanted one year after the first.

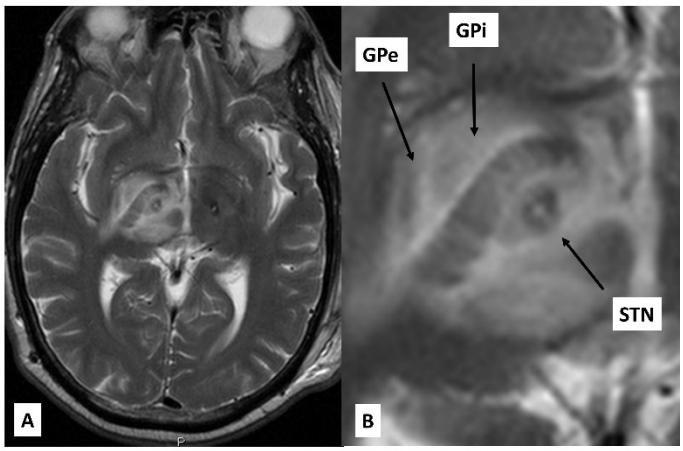

Figure 1: (A) Patient who had a unilateral infection of a DBS electrode which led to increased signal differentiation between the surrounding white matter tracts and visualization of the STN nucleus which is not visible on the contralateral side. (B) Enlarged view of infected side. STN: Subthalamic nucleus, GPi/GPe: internal and external globus pallidum.

The presumed vasogenic edema around the infected electrode highlighted the boundaries of the right subthalamic nucleus and adjacent deep brain anatomy in contrast to the unaffected, contralateral, left side (Figure 1). This observation led to the premise of this study, where we believe that the extracellular space could be manipulated experimentally to improve MRI visualization.

2.4. Part 1 Preclinical Animal Studies

2.4.1. Methods

Following UVA Institutional Animal Care and Use Committee approval (ACUC # 3843-08-10), Sus Scrofa Domestica (YorkShire) female pigs weighing approximately 25 pounds were acquired and acclimated in the vivarium facility for 3 days. The CED swine experiments were performed with 3T MRI utilizing a standard human head coil.

Before surgery, the infusion apparatus was prepared. A PHD Ultra syringe pump (*Harvard Apparatus*, Holliston, MA, USA) was used with a 500 microliter, airtight, glass syringe. The syringe was connected to a series of four 60-inch extension sets (*Medex Micro Bore,* Product Code 536020, Smiths Medical, Dublin, OH, USA), each of which had 0.4 ml priming volume. The extension sets were then connected to an EViTAR microcatheter. (*NexGen Medical Systems, Inc.*, Reno, NV, USA). In experiments where normal saline was infused, the system was primed with normal saline via a 3-way valve at an extension set connection point. Care was taken to ensure there were no air bubbles. When CSF was infused, the priming was performed in the same manner after CSF had been obtained by lumbar puncture in the anesthetized animal.

On the day of surgery anesthesia was induced, and a T2 3T MRI was obtained in three orthogonal directions (*Siemens Trio* with Numaris 4 B17 software, TR 6000, TE 93, 2mm slice width, no gap, resolution 320x320). The mid-thalamic targets were identified on these pre-surgical MR images and then compared to a published swine stereotactic atlas.[6,17] The coordinates for cannula placement were calculated and ranged in relation to the bregma: 0-3 mm anterior, 6-8 mm lateral, and 33-36 mm deep.

The animal was then positioned in a custom, MRI-compatible, stereotactic head frame such that the bregma and lambda points were aligned in the same plane. The scalp was then shaved and prepped with betadine, opened in linear fashion with a scalpel, and a small burr hole was created in the skull. After the dura was opened, the outer cannula of the infusion catheter, with a stylet, was then connected to the stereotactic manipulator and advanced to the target minus 1 cm in vector length (the infusion cannula is 1cm longer than the outer cannula). The outer cannula was then affixed to the skull. After removal of the stylet, the inner infusion microcatheter was then advanced through the outer cannula to the target. The PHD Ultra syringe pump was kept in the MRI control room and the tubing was passed through the wall. Sagittal, axial, and coronal T2 images were then obtained to verify the placement of the micro-catheter.

After MRI confirmation of the micro-catheter position, the infusion was instituted with rates between 1- 6 µL/min so that convective distribution would be achieved. MRI monitoring was obtained at consistent 15 minute intervals for a total of 90-120 minutes depending on the rate of infusion. The volume of distribution (Vd) was obtained by using the average diameter of the infusion front as measured from T2 signal changes.

Following completion of micro-infusion experiments and MR imaging, the infusion catheter was removed and the scalp was sutured closed. Animals were recovered with direct observation for evidence of behavioral, neurologic, or gait dysfunction. Necropsy was performed at either early (48 hours), subacute (1 week), or late (1 month) time points. The brains were formalin fixed for sectioning, gross inspection, and histology with immunohistochemistry by a certified neuropathologist. A total of seven animals were infused: five with normal saline and two with CSF. The summary is shown below in Table 1.

Table 1: Summary of Swine CED Experiments

#	Infusate	Rate	Observation/ Histology (Days)
1	NS	1µl/min x 45min, then 3 µ l/min for 45 min, then 6 µ l/min for 30 min	2
2	NS	3 µl/min x 90 min	28
3	NS	5 µl/min x 90min	7
4	NS	5 µl/min x 90min	28
5	NS	5 µl/min x 90min	7
6	CSF	5 µl/min x 90min	28
7	CSF	5 µl/min x 90min	7

NS: Normal Saline, CSF: Cerebrospinal Fluid

2.4.2. Results

Volume of Distribution

The Vd/Vi, measured from T2 weighted MRI sequences varied from 2 to 4.5 regardless of the infusate. The rate for CED (as opposed to diffusion) is generally accepted as greater than 0.05 µL per minute. These experiments infused between 1 to 6 µL per minute without noticeable differences in the Vd/Vi. Total volume of infusion was bounded by either MRI time for low flow rates (limited to 90 minutes), or by observing no further increase in the volume of distribution when a pial boundary was encountered, and this ranged from 90 to 360 µL.

MR Imaging

All MRI assessments were made from T2 weighted sequences. The CED infusions of normal saline or CSF became apparent with increased T2 hyperintensity after 30-45 µL as infused. By 90 µL, clear definition of nuclear structures began to develop. MRI changes in the infusion ceased when the infusion front reached the pial boundaries. CED infusions into the thalamus delineated the dorsomedial, ventral anterior, reticular, and centromedian nuclei – all of which were not apparent before the infusion (Figure 2). The enhanced appearance of the nuclear structures was consistent across animals with the ventral anterior and then the dorsomedial nucleus becoming the most apparent. Animal #7 had a post infusion scan performed 30 min after the completion of the infusion and the infusion effects persisted. Long term imaging was not performed.

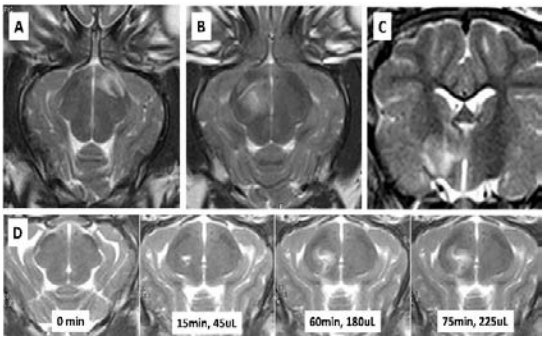

Figure 2: (A) axial view of animal #1 after 360 µL infusion of saline demonstrating the reticular nucleus is lateral to the VA nucleus, (B) axial view of animal #4 after 450 µL of saline, (C) coronal view of animal #6 after 450 µL CSF, and (D) axial time lapsed infusion of animal #3 at a rate 5 µL / min. The white matter tract medial to the VA nucleus, lateral to DM, and anterior to CM is readily apparent after infusion.

Histology

Histology was examined at either early (within 2 days), subacute (7 days), or late (28 days) time points for evidence of acute or latent infusion toxicity. All specimens were analyzed with Hematoxylin and Eosin stains. Animals infused with normal saline demonstrated mild neuronal effects with pyknotic neurons and axonal retractions – possibly attributed to the tonicity of the infusate (Figure 3). **Those infused with autologous CSF had no evidence of neuronal change at either time point: 7 and 28 days.**

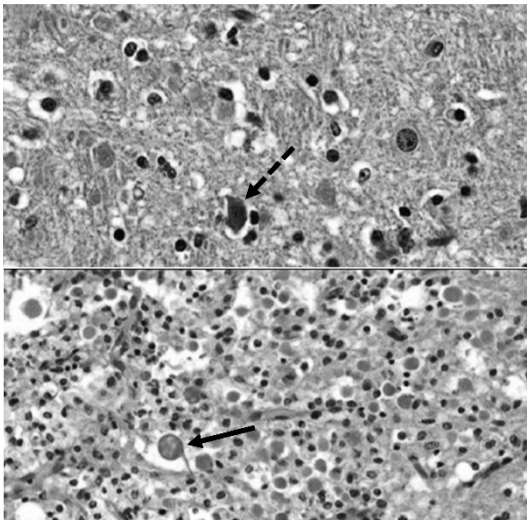

Figure 3: Hematoxylin and Eosin stains after convective infusion with normal saline identifying pyknotic neuron (*dashed arrow*) and axonal retraction figures (*solid arrow*) in a saline infused thalamus. These findings were not present when CSF infusion was performed.

2.5. Part 2 Preclinical Animal Studies

2.5.1. Purpose

Following the Part 1 preclinical animal studies, and FDA review, further infusions were performed to validate that there was no toxicity related to the infusion of CSF. A control site was included for comparison. The infusion catheter planned for the human trials was used in the Part 2 preclinical animal studies (SmartFlow™ K123605).

2.5.2. Methods

Following UVA Institutional Animal Care and Use Committee approval (ACUC # 3843-08-16), Sus Scrofa Domestica (YorkShire) female pigs weighing approximately 25 pounds were acquired and acclimated in the vivarium facility for 3 days.

On the day of surgery anesthesia was induced and a spinal tap was performed under fluoroscopic guidance. Five milliliters of CSF were removed and saved for later to be infused. The animal was then positioned in a custom stereotactic head frame such that the bregma and lambda points were aligned in the same plane. The scalp was then shaved and prepped with betadine, opened in linear fashion with a scalpel, and a small burr hole was created in the skull bilaterally 6mm lateral to the bregma. After the dura was opened, the infusion catheter (SmartFlow™ K123605) was advanced into the brain 30mm in the right thalamus then retracted (control site). It was then advanced 30mm in the left thalamus for the CSF infusion.

The previously acquired CSF was used to prime the infusion system. A Harvard Apparatus PHD Ultra infusion pump was used with a piece of extension tubing (*Medex Micro Bore,* Product Code 536020, Smiths Medical, Dublin, OH, USA) and a 500 microliter airtight gas syringe. The CSF was filtered with a 0.1 micron in-line filter while priming the system. CSF was then infused in the left thalamus at a rate of 5 microliters / min for a total volume of 450 microliters. The infusion catheter was then withdrawn, the wound was closed, and the animal was taken to recovery.

Nine animals in total were infused with autologous CSF. Five animals underwent necropsy at 24 hours and 4 animals underwent necropsy at 28 days. Necropsy was performed by removing the brain immediately following euthanasia via a craniectomy and placing the whole brain in 10% buffered formaldehyde.

After a minimum of 2 weeks the formalin fixed brains were cut, H&E stained, and analyzed by an independent neuropathologist.

2.5.3. Results

Histology results are summarized below. None of the CSF infusion sites had evidence of toxicity. Distinct tracts were identified in eight of the nine brains. In the brain where a tract was not identified, the thalamus was sectioned forty times in 5-micron thicknesses. After sectioning, slides were H&E stained then reviewed. All tracts showed typical findings of catheter insertion into brain (microhemorrhage at 24 hours; gliosis and hemosiderin deposition at 1 month). There was evidence of axonal injury in one acute animal control tract, consistent with severing of axons from the insertion of the CED catheter. The neuropathology report is attached as attachment 2.0.

	Animal #	CSF Infusion	Control
Acute (24 hours)	1	No neuronal injury, distinct track identified	Axonal swelling, distinct track identified
	4	No neuronal injury, distinct track identified	No neuronal injury, distinct track identified
	5	No neuronal injury, distinct track identified	No neuronal injury, distinct track identified
	8	No neuronal injury, distinct track identified	No neuronal injury, distinct track identified
	9	No neuronal injury, distinct track identified	No neuronal injury, distinct track identified
Chronic (1 month)	2	No neuronal injury, distinct track identified	No neuronal injury, distinct track identified
	3	No neuronal injury, no distinct track identified	No neuronal injury, no distinct track identified
	6	No neuronal injury, distinct track identified	No neuronal injury, distinct track identified
	7	No neuronal injury, distinct track identified	No neuronal injury, distinct track identified

3. STUDY OBJECTIVES

The proposed study will evaluate safety foremost but also the distribution and initial effectiveness of infusion-enhanced, MRI-guided DBS for patients with medication-refractory, Parkinson's disease.

3.1. Primary Objectives

Safety:

Safety of the CSF infusion will be evaluated using a common description of clinical complications for patients treated in this study. Safety will be determined by an evaluation of the incidence and severity of infusion-related side effects and complications from the first treatment day visit through the 6-month post–treatment time point. All AEs will be reported and categorized by investigators as definitely, probably, possibly, unlikely, or unrelated to the CSF infusion, and/or Parkinson's disease progression. Safety will be assessed by incidence and severity of AEs, changes in physical examinations, neurological exams, and the number of discontinuations due to AEs

3.2. Secondary Objectives

Distribution:

The volume of distribution (Vd) will be determined immediately following the infusion (Vi) with intraoperative 1.5T MRI, T2-weighted sequences. The distribution of the infusion by convective properties in a deep brain human nucleus (GPi or STN) will be determined by calculating the Vd/Vi ratio.

Efficacy:

The primary efficacy assessment will be measured with the unmedicated UPDRS, motor subsection (part III) at 6 months in comparison to baseline. Additional efficacy endpoints will include standard, validated assessments of PD before and after DBS. Standard clinical measures of PD will be obtained as per usual clinical protocol at pretreatment baseline and 6 months postoperatively. These DBS-related assessments include:

- UPDRS in the off and on medication state
- Levodopa medication equivalents (milligrams)
- Neuropsychological assessment
- PDQ-39

4. SUBJECT ELIGIBILITY

Patients with medically-refractory Parkinson's disease who are planned for MRI-guided DBS surgery under general anesthesia are candidates for this protocol. They will be invited to participate in this study if they decide to have DBS surgery in the intraoperative MRI suite under general anesthesia. Patients who decide to have awake DBS surgery with clinical and electrophysiologic testing will not be eligible. The consenting process will occur in the outpatient clinic setting, and patients will have the opportunity to review the consent document at home with their families. A total of eight patients will be enrolled.

4.1. Inclusion Criteria

1. Men and women, age 30 years and older
2. Subjects with advanced PD who are scheduled for MRI-guided DBS surgery under general anesthesia
3. Subjects who are able and willing to give informed consent and able to attend clinic visits through 6 months
4. The target nucleus, GPi or STN, is visible on MRI so that it can be targeted for the study infusion and then for MRI-guided DBS

4.2. Exclusion Criteria

1. DBS surgery planned in the awake condition with microelectrode recordings and clinical testing
2. Spinal pathology not amenable to lumbar puncture
3. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
4. Legal incapacity or limited legal capacity as determined by the neuropsychologist
5. Are participating or have participated in another clinical trial in the last 30 days
6. Any illness that in the investigator's opinion preclude participation in this study.
7. Subjects who are prisoners.
8. Women who are pregnant.

9. Subjects who do not speak English. (Questionnaires are validated in English and no other language.)

5. TREATMENT PLAN

5.1. Study Overview

This will be an open-label, single-arm, pilot study investigating the safety and feasibility of infusion-enhanced, MRI-guided DBS electrode placement. We intend to enroll patients, with Parkinson's disease and medically-refractory motor symptoms, who are already planned for MRI-guided DBS electrodes under general anesthesia. The *hypothesis* of the study is that a convective micro-infusion of autologous CSF will enhance the T2-weighted MRI visualization of the targeted nucleus during image-guided DBS surgery for Parkinson's disease. We will record standard clinical measures of PD at baseline and 6 months following DBS surgery. The study will recruit patients at a rate of approximately one a month and will take less than two years to complete.

5.2. Treatment Assignment

All subjects will receive the CSF infusion during the DBS surgery. The DBS surgery will be performed on the targeted nucleus either bilaterally or unilaterally, as previously determined by a multidisciplinary team of neurology, neurosurgery, and neuropsychology. During unilateral DBS surgery, the targeted nucleus will be infused using CED. The nondominant side will be infused during a bilateral DBS procedure.

5.3. DBS Surgery and Treatment Administration

5.3.1. Pre-surgical evaluation

Patients will undergo standard pre-surgical evaluations in preparation for surgery at the same time as their baseline assessment. This will include preoperative visits with the neurosurgeon and anesthesia team at the Preanesthesia Evaluation and Testing Center (PETC). Patient history will be taken with regards to any recent changes in medical status and a review of current medications both prescription and over-the-counter will be obtained by a qualified sub-investigator. Patients taking aspirin, other non-steroidal anti-inflammatory medications and vitamin supplements that include vitamin E will have been counseled to stop taking these at least 7 days before surgery which is our standard clinical practice for DBS surgery. Routine labs, including complete blood count with platelets, blood chemistries, PT/PTT, pregnancy test for women of childbearing age and urinalysis will be obtained, as well as 12 lead electrocardiogram and plain film chest radiograph when indicated. Additional studies specific to certain medical conditions and/or to ensure patient safety may also be obtained. The results of this detailed assessment will be recorded in written form on case report forms and recorded in the patients electronic medical record. Subjects will be instructed to be NPO and hold their PD medications after midnight prior to the surgery.

Table 2: Treatment day procedures

DBS surgery	Presurgical admission	Clinical practice
	General anesthesia	
	Reference MRI for stereotactic planning	
	Surgery for frontal burr hole	
	Stereotactic insertion of guide cannula	
Infusion	Lumbar puncture for 10 ml CSF	Research
	Insertion of microcatheter to unilateral GPi or STN	
	CED infusion of autologous CSF (<0.5 ml)	
	MRI monitoring of infusion	
Completion DBS	Replacement of microcatheter with DBS electrode	Clinical practice
	Wound closure	
	Implantation of pulse generator	

5.3.2. Initial DBS surgery

Patients will present to the pre-surgical area having not eaten since midnight and off all PD medications. They will be checked in by the pre-surgical staff, which includes placement of an intravenous line, baseline vital signs, and medication reconciliation as standard of care. After meeting with the anesthetic and surgical teams, the patient will be taken back to the operating room for general anesthesia and intubation. A lumbar puncture will be performed to obtain up to 10 ml of autologous CSF. This will be passed through a sterile 0.1 micron filter and maintained sterile.

Patients will then undergo MRI-guided DBS surgery in the intraoperative MRI suite (IMRIS) according to standard practice. Clinically, we utilize frameless stereotaxy (*ClearPoint*, *MRI Interventions*) for the surgery. A 1.5T reference MPRAGE MRI is acquired and then fused with preoperative 3T MRI of the designated target. GPi is optimally visualized with inversion recovery sequence and STN is best imaged with a T2 sequence. (The choice of stereotactic target, either globus pallidum or subthalamus, is a predetermined clinical decision made by a multidisciplinary team of neurology, neurosurgery, and neuropsychology.) The stereotactic trajectory is planned on a neuronavigation workstation by direct MRI visualization of the target nucleus: GPi or STN.

The scalp is prepped and draped and local anesthetic is infiltrated into the frontal incision. The incision is opened and a pre-coronal, frontal burr hole is drilled corresponding to the designated entry point from the stereotactic coordinates. A closed-dura technique is utilized to minimize loss of CSF and brain shift. A scalp mounted stereotactic frame (*MRI Interventions*) is attached to the burr hole. The bore of the magnet is draped with sterile technique, and the patient is moved into the bore of the magnet for the stereotactic portion of the surgery that is MRI guided and monitored.

5.3.3. Infusion Procedure

Once the patient is positioned within the MRI, the dura is sharply punctured with a sharp, ceramic stylet, and the MR-compatible infusion catheter is inserted. A second MRI is obtained to confirm the catheter position.

The research infusion of autologous CSF is initiated at 5 microliters/minute. Serial MRI monitoring of the infusion is obtained with T2 weighted images at approximately 15 minute intervals until the target nucleus can be visualized or until a total of 500 microliters is administered. The research infusion could add up to an additional 100 minutes to the patient's DBS surgery. MR imaging of the research infusion and then clinical assessment of the DBS electrode placement will be conducted on a 1.5T Siemens Espree system with continuous monitoring of both SAR and B1+rms values.

A Medfusion 3500 syringe infusion pump with a 1.0 milliliter BD glass syringe will be used with extension tubing (*Medex Micro Bore,* Product Code 536020, Smiths Medical, Dublin, OH, USA). The infusion catheter will be the SmartFlow™ K123605 (MRI Interventions).

5.3.4. Completion of DBS procedure

The microcatheter is removed, and replaced with the DBS electrode. There is no intraoperative, macrostimulation testing of the DBS electrode as the patient is asleep and electrode position is based on MRI targeting. The electrode is anchored in place, and the wound is closed. For bilateral cases, the contralateral (dominant side) DBS electrode will be inserted as per standard practice without the research infusion protocol.

The second stage of the DBS procedure is then performed on the same day and under the same general anesthetic for placement of the implanted pulse generator. For this, the patient is repositioned in a supine fashion with their head slightly rotated away from the pulse generator site. The ipsilateral scalp, neck, and chest are prepped and draped. The cranial incision is reopened and a small counter incision is made behind the ear. A subcutaneous pocket is made at the clavicular level. The DBS lead extension is tunneled

subcutaneously between the head and chest, such that the appropriate connections can be made from the DBS electrode to the lead extension and then to the pulse generator. Intraoperative lead impedance test is performed to confirm the electrical integrity of the system. The wounds are then copiously irrigated with antibiotic saline and closed. The patient is taken to the recovery area following extubation. Medications are reinstituted, and they are observed overnight on a neurosurgical ward for one or two nights. Postoperative MRI is obtained standard of care, and the DBS system is maintained off until programming in the clinic. At the University of Virginia, we routinely perform a postoperative MRI after DBS surgery to assess the final position of the electrode. The imaging is conducted within the conditional limits set forth by the FDA for DBS systems. The final DBS system implanted will be assessed with MRI in one of two scenarios:

DBS systems that are full-body eligible:

- Neurostimulator models 37612 Activa RC, 37603 Activa SC, 37601 Activa PC
- No pocket adaptor can be implanted with the DBS system.
- Fully-implanted leads (ie, leads that are internalized and capped)
- No open or short circuits

DBS systems that are head-only eligible:

- Neurostimulator models 37602 Activa SC, 7428 Kinetra, 7426 Soletra
- Any DBS system that is implanted with a pocket adaptor
- Partially-implanted leads (ie, leads that are externalized)
- No open or short circuits

5.3.5. DBS programming and outpatient follow-up

The following is the standard clinical protocol for DBS programming in the outpatient setting: The wound is assessed at seven to ten days and surgical clips are removed. The DBS pulse generator is turned on at one month. For this first programming session, all patients present without having taken their PD medications since midnight. Each of the four DBS contacts is tested by escalating the stimulation to either symptom response or the induction of stimulation-induced side effects. High frequency stimulation is used at either 130 or 180 Hz. The optimal electrode configuration is selected, and then the patient takes their routine oral PD medications. They are observed for an hour for potential side effects with stimulation plus medication. Standard neurologic measures and PD assessments are performed in the clinic during stimulation testing. These include testing for tremor, bradykinesia, and gait. The patient is observed for potential dyskinesia after taking their medications. Follow up programming visits are then scheduled for two and three months postoperatively. At this time, stimulation and medications will be titrated for an optimal symptoms response. A full UPDRS assessment in the on and off state will be obtained at six months.

The patient and their caregiver will be trained in the management of the DBS device. They may have some ability to adjust the DBS amplitude within the parameters set by the neurologist. They will be able to interrogate their system at any time, and can disable the device in the event of an emergency. They will be instructed about the issues of an implanted pacemaker device, and to be cautious of strong magnetic fields.

As part of this research protocol, adverse events will be recorded during this first programming visit and each subsequent visit.

5.4. Concomitant Medications/Treatments

Prohibited Medications

Patients taking aspirin, other non-steroidal anti-inflammatory medications and vitamin supplements that include vitamin E will have been counseled to stop taking these at least 7 days before surgery. These medicines are contraindicated for DBS surgery.

Concomitant Medications

All medications and other treatments taken by a subject beginning at the baseline visit and continuing throughout the subject's participation in the study will be recorded on the Concomitant Medication CRF. Thereafter, Concomitant Medications information will not be collected or recorded in the eCRFs. The information documented will include the medication name, indication, dosage, and the dates of start and discontinuation.

At each visit, the site will obtain a complete listing of all medications currently being taken by the subject. Any changes, additions or deletions in the administration of concomitant medications will be recorded on the Prior and Concomitant Medications CRF. This information will also be documented in the subjects electronic medical record. Subjects may receive medications to treat safety events and routine treatment for underlying medical conditions as deemed necessary by the Investigator.

5.5. Duration of Study Participation

Subjects who are enrolled will be followed for six months after their DBS surgery. The Screening and Baseline period is a maximum of 90 days before the surgery and CED infusion. The follow-up period is the first 6 months post-DBS implantation. Follow up clinic visits correspond with routine post DBS clinic follow up and does not include additional visits specific to this research.

5.6. Discontinuation/Withdrawal from Study

Subjects may withdraw or be discontinued from the study at any time for any of the following reasons:

- Disease progression
- Inter-current illness that prevents further treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study
- Subject does not comply with study procedures (i.e. missed follow-up visits)
- At the discretion of the investigator
- Death

5.7. Subject Status Definitions

Enrolled: All subjects who sign an informed consent will be considered enrolled in the study. All subjects consented on the study will be assigned to the research study in EPIC.

Screen Failure: A subject who is withdrawn or discontinues from the study prior to receiving DBS is considered a screen fail. Screen failures are not considered a study accrual and will be replaced. Note: The IRB defines any individual that has signed an informed consent as an enrollment in this study and so screen failures should be reported to the IRB with enrollment numbers.

On-Study: A subject is considered on-study on the date when the study team has confirmed the subject has met all of the inclusion and none of the exclusion criteria, and the treating physician/surgeon or study PI has signed off on the confirmation.

On-Treatment: A subject is considered on-treatment on the date that the DBS surgery is initiated. A subject who is withdrawn or discontinues from the study after receiving DBS surgery is considered a discontinuation and will not be replaced.

On Follow-up: A subject is considered on follow-up on the date that the DBS surgery is completed.

Off-Study: A subject is considered off-study if they are removed from the study for any of the reasons listed in Section 4.6, or if they have completed all study assessments through follow-up (6 Month follow-up visit).

6. DEVICE INFORMATION

Description

The agent under investigation is an intracerebral infusion of autologous CSF. The autologous CSF will be obtained via lumbar puncture and administered during the same procedure, so there is no need for storage of the CSF.

Agent Preparation and Administration

A lumbar puncture will be performed to obtain 10 ml of autologous CSF. This will be passed through a sterile 0.1 micron filter and maintained sterile. A disposable, MRI-compatible frameless stereotactic system that is employed for MRI-guided DBS surgery under general anesthesia will be secured to the patient's skull. Once the patient is positioned within the MRI, the dura is sharply punctured with a sharp, ceramic stylet, and the MR-compatible infusion catheter is inserted.

The research infusion of autologous CSF is initiated at 5 microliters/minute. Serial MRI monitoring of the infusion is obtained with T2 weighted images at 15 minute intervals until the target nucleus can be visualized or until a total of 500 microliters is administered. Any remaining CSF will be disposed of at the end of the procedure.

A Medfusion 3500 syringe infusion pump with a 1.0 milliliter BD glass syringe will be used with extension tubing (*Medex Micro Bore,* Product Code 536020, Smiths Medical, Dublin, OH, USA). The infusion catheter will be the SmartFlow™ K123605 (MRI Interventions).

7. EVALUATION AND ASSESSMENTS

7.1. Schedule of Events

The following table shows the standard of care and research assessments that will be performed throughout the study.

	Screening and Baseline*	**DBS Surgery**	**One Month (± 2weeks)**	**6 Months (± 1 month)**
Informed Consent	X			
Review study eligibility	X			
Medical History	X			
MRI	X	X		
Vital signs	X	X		

PDQ-39*	X			X
Physical Exam	X			
Neurological Exam	X		X	X
Clinical Labs	X			
Lumbar Puncture and CED infusion		X		
Neuropsychological Evaluation	X			X
UPDRS	X			X
Review of PD medications	X			X
Adverse Event assessment		X	X	X

*Screening and Baseline assessments will be performed up to 90 days prior to DBS surgery. Standard of care procedures completed within this period but prior to consent may be used for the purposes of the study. The order of screening/baseline procedures will vary, but all tests required for eligibility must be complete prior to confirmation of eligibility.

Please note that any assessments done as part of the patient's standard care need not be performed by an investigator, as long as the assessor is qualified and regularly performs this type of assessment as part of their regular medical center duties. The results of the standard tests and any abnormal findings will be reported back to the principal investigator to be evaluated and reported for the research.

7.2. Study Assessments

7.2.1. Medical History

A medical history should be obtained during the screening/baseline visit to establish baseline medical condition for evaluation of AEs. Medical history includes clinically significant diseases, surgeries, history of cancer, brain injuries, and heart conditions. A start date (year), end date (year) and any medications or surgeries to treat the condition will be recorded. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient at the time of the assessment for any reason will be collected at this time.

7.2.2. MRI

For the purpose of this study, MR Exams without contrast will be performed. The MR Imaging should include T1, T2, and DTI sequences. In addition, MR Images: DWI (including ADC maps, which allows differentiation between lesion cytotoxic edema-low ADC and vasogenic edema around the lesion-high ADC) will be obtained at baseline.

7.2.3. Vital Signs

Vital signs including respiratory rate, pulse rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP] and body temperature, will be collected at Screening/Baseline assessment and during CED infusion. Vital signs will be continuously monitored during the DBS surgery. At the Screening/Baseline visit, it is recommended that vital signs be assessed in subjects who have been in a seated resting position for at least 3 minutes. Transient changes in BP, HR, or RR may be expected. If a subject has symptoms that appear to be related to changes in BP, HR, or RR, all changes deemed by the Investigator to be of clinical importance should be reported as an AE.

7.2.4. PDQ-39 Questionnaire

A self reported Parkinson's Disease Questionaire (PDQ-39) will be completed at Screening/Baseline as well as 6 Months FU as a secondary measure of effectiveness.

7.2.5. Physical Exam

A full physical examination will be performed at the Screening/Baseline visit only. Physical examinations will include examination of the following body systems: general appearance (including height and body weight), skin, neck, HEENT (head, ears, eyes, nose and throat), heart (auscultation of heart sounds), lungs (auscultation of lung fields), abdomen palpation and auscultation of bowel sounds, lymph nodes, extremities, and nervous system.

An abbreviated, symptom-directed physical exam will be performed at all other assessments. Any abnormal findings which were not noted at the baseline assessment must be reported as an AE.

7.2.6. Neurological Exam

A full neurological exam will be performed at the Screening/Baseline visit and at the 1 and 6 Month follow up visits for adverse event determination. Neurological examinations will include orientation, sensory (pain, position, vibration, and light touch), reflexes (biceps, triceps, knees, ankles and pathological). Coordination and balance will be tested by performing Finger to Nose, Heel to Shin, Rapid Alternating Movements, Heel-to-toe walking, and Romberg's test assessments. In addition, motor, strength and gait testing will be performed.

7.2.7. Laboratory Parameters

Blood samples for clinical labs will be obtained at the Screening/Baseline visit to determine eligibility for DBS surgery. The following clinical laboratory tests should be performed as per standard of care:

Hematology

- Hemoglobin
- Hematocrit
- Total leukocyte count and differential
- Platelet count

Serum Chemistry

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma-glutamyl transferase (GGT)
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Lactate dehydrogenase (LDH)
- Creatinine
- Blood urea nitrogen (BUN)
- Blood glucose
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Calcium

- Phosphorus

Clotting Time

- Prothrombin time (PT)
- Partial Thromboplastin Time (PTT)

Pregnancy Test

7.2.8. Neuropsychological Assessment

A standard neuropsychological assessment will be conducted prior to DBS surgery and will be repeated at the 6 month follow up visit for potential cognitive and psychological effects of the surgery.

7.2.9. Unified Parkinson's Disease Rating Scale

The Unified Parkinson's Disease Rating Scale (UPDRS) will be performed at Screening/Baseline, and at the 6 Month Follow Up visit to assess the patient's motor symptoms. Each treated subject will be examined "off medication" and "on medication" by a qualified movement disorders specialist.

7.3. Final Study Visit

The final study visit will occur at the 6 Month Follow Up visit. All final efficacy assessments will be collected at this visit. Any ongoing adverse events will be followed at the routine annual clinic visit.

7.4. Early Termination Visit

In the event that a subject does not want to continue in the study until the 6 Month Follow Up visit, every effort will be made to complete a a visit where final AE determination will be made. Subjects may withdraw voluntarily from participation in the study at any time. The subject will continue to be monitored on an annual basis as part of routine clinical care.

8. DATA ANALYSIS PLAN

For this study, the Safety and Effectiveness assessment will be descriptive with no statistical endpoints. The results will be examined and analyzed and used as a basis for determining the nature of future studies. Formal hypothesis testing for efficacy is not proposed for this initial safety and preliminary efficacy trial.

8.1. Safety

The PI will evaluate all AE's that occur throughout the study and provide his assessment of the study safety profile as well as his recommendations for the study continuation. All AEs will be communicated to the FDA as part of the annual reporting for this proposed IDE study.

All AEs will be reported and categorized by investigators as definitely, probably, possibly, unlikely, or unrelated to the CSF infusion, and/or Parkinson's disease progression. Standard Code of Federal Regulation definitions for Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) will be used in assessment of AEs.

Primary safety endpoint for this study is the adverse event profile generated during the CED procedure through Month 6.

8.2. Efficacy

The primary efficacy endpoint will be focused on determining the degree of change in motor symptoms as measured from the un-medicated (*off*), UPDRS motor subsection (Part III) at 6 months in comparison to baseline by a movement disorder neurologist.

8.3. Additional Evaluations

Additional measures of safety will be obtained during the study. These secondary measures of safety will include evaluations post-treatment which are compared to a baseline assessment. These measures include:

- Neuropsychological assessment for cognition, depression, and behavioral changes at scheduled visits
- Adverse events
- Physical exam
- Neurological exam

Secondary efficacy endpoints will include comparison of Baseline to post-treatment assessments for:

- Levodopa equivalent medication usage (milligrams)
- Quality of life assessment with PDQ-39

8.4. Statistical Considerations and Sample Size

This is an open-label feasiblity study of 4 subjects to be recruited from a single center. In order to find 4 eligible subjects suitable for treatment, up to 20 subjects may be consented and screened. For this study, a statistical sample size analysis is not proposed. All those subjects that were consented and then found not meeting study requirements will be considered screen failures.

The Safety and Effectiveness assessment will be descriptive with no statistical endpoints. The results will be examined and analyzed and used as a basis for determining the nature of future studies.

9. ADVERSE EVENT AND REPORTING

The adverse event collection interval for this study begins at the time of the lumbar puncture (start of investigational procedure) and ends at the 6 Month Follow up visit.

After informed consent has been obtained, and prior to initiation of investigational intervention, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as blood draw). AEs reported between the time the patient signed the informed consent and the DBS surgery will be captured as concurrent medical history unless due to a protocol-related procedure.

After initiation of investigational intervention, all adverse events will be reported according to the guidelines in the following sections. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to the investigational intervention.

All adverse events, whether reported by the patient or noted by study personnel, should be recorded in the patient's medical record. Adverse events should be assessed for seriousness, severity, attribute and expectedness by the Principal Investigator, or designee.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of study intervention, or those experiencing AEs that are present at the end of their participation in the study. Such subjects should receive post-treatment follow-up as appropriate.

If an ongoing AE changes in its severity or in its perceived relationship to study intervention, a new AE entry for the event should be completed.

AE and SAE recording will continue until the End of Treatment visit is performed. SAEs considered related to the interventional procedure may be reported at any time, even after the patient's final visit.

9.1. Definitions

Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an investigational intervention, whether or not related to the investigational intervention(s). Medical conditions present before starting the investigational intervention will be considered adverse events only if they worsen after starting study treatment. Adverse events include unfavorable, harmful or pathological changes in the general condition of a subject; subjective or objective symptoms (spontaneously offered by the subject and/or observed by the Investigator or the study nurse); intercurrent events or exacerbation of pre-existing diseases which occurred after the administration of the study drug; clinically significant changes in laboratory abnormalities; or any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

Persistent or Recurrent Adverse Events

A persistent adverse event is an event which extends continuously, without resolution, between assessments. This event should only be recorded once with the initial severity grade. If the severity of the event worsens, then the original event ends and a separate event is recorded at the greater grade.

A recurrent adverse event is an event which resolves between assessments and subsequently recurs. This should be recorded as a separate event for each recurrence.

Secondary Adverse Events

In general, events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be considered a single event identified by the primary cause. However, a secondary event should be listed as an independent event if it meets one of the following criteria:

- severe
- serious
- separated in time from the primary event

If it is not clear as to whether events are dependent, then record as separate adverse events.

Abnormal Laboratory Values/Clinical Assessments

It is the responsibility of the investigator, or designee, to review and document all laboratory findings and clinical assessments, which may include vital signs, physical exams and ECGs. Medical and scientific judgment should be exercised in deciding whether a laboratory abnormality or clinical finding should be classified as an adverse event. In general, an abnormal laboratory test result or clinical finding should be considered as an adverse event if it meets at least one of the following criteria:

- Is associated with clinical symptoms
- Results in a change in study treatment (e.g., treatment modification, interruption or discontinuation)
- Requires a medical intervention or change in concomitant therapy
- Clinically significant in the investigator's judgment

Note that if a clinically significant laboratory abnormality or clinical finding is a sign of a disease or syndrome (e.g. elevated ALT) then this should be recorded as a single event identified by the diagnosis (hepatic failure).

If a clinically significant laboratory abnormality is not a sign/symptom of another primary event, the abnormality itself should be recorded as an adverse event. The event should be described using a specific clinical term ("hyperkalemia"), if possible, or as test result above or below the normal range (e.g., "elevated Vitamin D," as opposed to "abnormal Vitamin D").

Death

Death should be considered an outcome of an adverse event and not an independent adverse event. The event or condition that caused the death should be recorded as the adverse event with the outcome of death. If the cause of death is unknown and cannot be ascertained at the time of reporting, then the event should be reported as an **"unexplained death"**. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be updated by the established cause of death.

Preexisting Medical Conditions

A preexisting medical condition is one that is present during the pre-study screening assessments. These conditions should be noted on the Medical History form. Preexisting medical conditions are not considered adverse events unless any of the following characteristics worsen following initiation of any study-related procedure:

- frequency
- severity
- character

  If any of the above conditions apply, then this should be recorded as an adverse event. Remember to convey that this is a change in a preexisting condition when describing the event (e.g., "increased frequency of kidney stones").

Adverse Device Effect (ADE)

An adverse device effect (ADE) is any untoward and unintended response to a medical device. This definition includes:

- - any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device,
- - any event that is a result of a user error

Serious Adverse Device Effect (SADE)

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated Adverse Device Effect (UADE)

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

Serious Adverse Event

A serious adverse event or experience (SAE) is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- Fatal;
- Life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant disability/incapacity;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

  *Hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event, except if the hospitalization meets at least one of the following criteria:

- The hospitalization is less than 24 hours without an admission
- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not suffered an adverse event.

  If the hospitalization meets any of these criteria, then it is not considered a serious adverse event.

9.2. Attribution Assessment

The Principal Investigator, or designee, will evaluate all AEs and assess their toxicity and attribution, if any, to study drug. The following criteria will define the attribution:

Definite: The AE is clearly in relation to the investigational intervention.
Probable: The AE is likely related to the investigational intervention.
Possible: The AE may be related to the investigational intervention.
Unlikely*:* The AE is doubtfully related to the investigational intervention.
Unrelated*:* The AE is NOT related to the investigational intervention.

9.3. IRB Reporting Requirements

Serious and unexpected adverse events must be submitted to the site Institutional Review Board according to the participating site institutional policies.

For the University of Virginia clinical site, the Principal Investigator (PI) or designee is responsible for reporting AEs and unanticipated problems to the UVA HSR-IRB according to the following guidelines.

Table 1. IRB Reporting Requirements

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event *See Oncore reporting requirement (sponsor's protocol section 10.5).*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by you sponsor, if applicable.)* Or Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

9.4. Additional Reporting Requirements

9.4.1. Reporting to the FDA

The Sponsor for the study (the UVA PI or designee) is responsible for providing safety updates to the FDA per the following guidelines. The reporting times refer to the time the study team received knowledge of the AE.

Table 2. FDA Reporting Requirements

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibl related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IND annual report

9.4.2. Data Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial.

9.5. Expected adverse events

All events that are commonly seen in this patient population or in patients who have DBS may be reported as expected. The patient will undergo two procedures during the course of this study that differ from the standard clinical practice of MRI-guided placement of DBS electrodes under general anesthesia. They are a lumbar puncture and an intracerebral infusion of autologous CSF. Adverse events described here and in the informed consent may also be considered expected.

Lumbar puncture

Obtaining a lumbar puncture leads to the risk of complications of the lumber puncture which include bleeding, infection, nerve root damage, CSF leak, bowel or bladder incontinence, weakness, sensory loss, need for operation to repair CSF leak or evacuate hematoma. Lumbar punctures are a standard procedure used for many indications; the risk of a complication is minimal. Discomfort from the procedure should be minimal as the procedure is being performed while the patient is under general anesthesia. Patients with known spinal pathology will be excluded to minimize the risk of complications associated with the lumbar puncture. In the event that CSF cannot be obtained or the fluid obtained is excessively bloody, then the infusion procedure will be aborted and the DBS electrodes will be placed using standard techniques. Patients will be fully informed of the risks of lumbar punctures during the consenting process.

Intracerebral infusion

The primary risk of the intracerebral infusion is that the infusion of autologous CSF will lead to neuronal damage. This risk is assessed to be minimal based on our preclinical animal studies demonstrating no acute and chronic histologic effects as a result of the infusion of CSF in swine. Our results are similar to other results in a rat model where albumin was infused and no damage was noted.[3] In order to mitigate the risk for toxicity, we plan to limit the infusion to a maximum volume of 500 microliters of autologous CSF. However, if unforeseen neuronal damage were to occur, there could be damage to the target structures and the surrounding structures leading to loss of sensation, worsening of movement disorders, and weakness. Patients will be fully informed of the risks of the CSF infusion during the consenting process.

Catheter insertion

The insertion of the infusion catheter into the brain could also lead to brain injury from intracerebral bleeding or stroke. This risk should not be increased beyond that for routine DBS surgery as the microcatheter will be inserted through a guide cannula that is already positioned for the DBS electrode. Typically, the risk of a hemorrhagic complication from stereotactic insertion of an electrode is ~1%.[5] Potentially, fewer DBS electrode passes will be required with the improved imaging leading to an overall reduced risk than traditional, awake DBS surgery where multiple microelectrodes are inserted to map the target nucleus.

10. STUDY MANAGEMENT

10.1. Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to all ICH E6 principles and Good Clinical Practice (GCP), to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

10.2. Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.3. Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB-HSR approval/favorable opinion.

For any such emergency modification implemented, a UVA IRB modification form must be completed by study Personnel within five (5) business days of making the change.

10.4. Other Protocol Deviations/Violations

Protocol Deviations: A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

Study personnel will record the deviation, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Violations should be reported by study personnel to the IRB within one (1) week of the investigator becoming aware of the event.

10.5. Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until six years after the completion and final study report of this investigational study.

10.6. Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations, all applicable local regulatory laws and regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. It is the responsibility of the Principal Investigator to ensure that all study site personnel are aware that the study protocol and all data generated is confidential and should not be disclosed to third parties (with the exception of local and national regulatory bodies which require access for oversight purposes).

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11. REFERENCES

1. Black PM, Moriarty T, Alexander E, 3rd, Stieg P, Woodard EJ, Gleason PL, et al: Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications. **Neurosurgery 41:**831-842; discussion 842-835, 1997
2. Burchiel KJ, McCartney S, Lee A, Raslan AM: Accuracy of deep brain stimulation electrode placement using intraoperative computed tomography without microelectrode recording. **J Neurosurg 119:**301-306, 2013
3. Ding D, Kanaly CW, Cummings TJ, Herndon JE, 2nd, Raghavan R, Sampson JH: Long-term safety of combined intracerebral delivery of free gadolinium and targeted chemotherapeutic agent PRX321. **Neurol Res 32:**810-815, 2010
4. Elias WJ, Fu KM, Frysinger RC: Cortical and subcortical brain shift during stereotactic procedures. **J Neurosurg 107:**983-988, 2007
5. Elias WJ, Sansur CA, Frysinger RC: Sulcal and ventricular trajectories in stereotactic surgery. **J Neurosurg 110:**201-207, 2009
6. Felix B, Leger ME, Albe-Fessard D, Marcilloux JC, Rampin O, Laplace JP: Stereotaxic atlas of the pig brain. **Brain Res Bull 49:**1-137, 1999
7. Hall WA, Martin AJ, Liu H, Nussbaum ES, Maxwell RE, Truwit CL: Brain biopsy using high-field strength interventional magnetic resonance imaging. **Neurosurgery 44:**807-813; discussion 813-804, 1999
8. Ivan ME, Yarlagadda J, Saxena AP, Martin AJ, Starr PA, Sootsman WK, et al: Brain shift during bur hole-based procedures using interventional MRI. **J Neurosurg 121:**149-160, 2014
9. Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, et al: Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. **Mov Disord 21 Suppl 14:**S290-304, 2006
10. McClelland S, 3rd, Ford B, Senatus PB, Winfield LM, Du YE, Pullman SL, et al: Subthalamic stimulation for Parkinson disease: determination of electrode location necessary for clinical efficacy. **Neurosurg Focus 19:**E12, 2005
11. Mirzadeh Z, Chapple K, Lambert M, Evidente VG, Mahant P, Ospina MC, et al: Parkinson's disease outcomes after intraoperative CT-guided "asleep" deep brain stimulation in the globus pallidus internus. **J Neurosurg 124:**902-907, 2016
12. Ostrem JL, Galifianakis NB, Markun LC, Grace JK, Martin AJ, Starr PA, et al: Clinical outcomes of PD patients having bilateral STN DBS using high-field interventional MR-imaging for lead placement. **Clin Neurol Neurosurg 115:**708-712, 2013
13. Patel NK, Plaha P, Gill SS: Magnetic resonance imaging-directed method for functional neurosurgery using implantable guide tubes. **Neurosurgery 61:**358-365; discussion 365-356, 2007
14. Sillay KA, Rusy D, Buyan-Dent L, Ninman NL, Vigen KK: Wide-bore 1.5 T MRI-guided deep brain stimulation surgery: initial experience and technique comparison. **Clin Neurol Neurosurg 127:**79-85, 2014
15. Starr PA, Markun LC, Larson PS, Volz MM, Martin AJ, Ostrem JL: Interventional MRI-guided deep brain stimulation in pediatric dystonia: first experience with the ClearPoint system. **J Neurosurg Pediatr 14:**400-408, 2014
16. Starr PA, Martin AJ, Ostrem JL, Talke P, Levesque N, Larson PS: Subthalamic nucleus deep brain stimulator placement using high-field interventional magnetic resonance imaging and a skull-mounted aiming device: technique and application accuracy. **J Neurosurg 112:**479-490, 2010
17. Sudhyadhom A, Okun MS, Foote KD, Rahman M, Bova FJ: A Three-dimensional Deformable Brain Atlas for DBS Targeting. I. Methodology for Atlas Creation and Artifact Reduction. **Open Neuroimag J 6:**92-98, 2012

18. Vega RA, Holloway KL, Larson PS: Image-guided deep brain stimulation. **Neurosurg Clin N Am 25:**159-172, 2014