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## Form B: Medical IRB Research Description

### **Continuation of a Pilot Study to Evaluate the Safety and Feasibility of Implanting Autologous Peripheral Nerve Grafts into the Substantia Nigra of Subjects with Parkinson's Disease Undergoing Deep Brain Stimulation Surgery and Treatment**

**1. Background:** PD results from the progressive degeneration of dopaminergic neurons within the substantia nigra pars compacta (SNpc). No current treatment halts or reverses the ongoing degeneration or loss of cell function. PD is a complex, chronic, neurodegenerative disorder that occurs worldwide and affects up to one million Americans (Parkinson's Disease Foundation, 2011). It is well established that the symptoms of PD, tremor, rigidity, and slowness of movement, result from the progressive degeneration of dopaminergic neurons within the SNpc deep in the midbrain. Unfortunately, the cause of the degeneration remains unknown. While existing pharmaceutical and surgical therapies have some impact on the symptoms of PD, there is no current therapy that stops or reverses the ongoing loss of cell function, deterioration, and ultimate cell death. Early preventative intervention is difficult because symptoms of PD do not begin until 75-80% of the dopaminergic neurons have lost measurable function. However, there is evidence to suggest that a proportion of these cells are off-line and non-functional but not dead.

This pilot study is designed to follow up on a previous, preliminary study and test the long-term safety and feasibility of the implantation of autologous peripheral nerve grafts into the substantia nigra pars compacta (SNpc) of participants with PD undergoing deep brain stimulation (DBS) surgery. Peripheral nerve tissue contains Schwann cells which produce growth factors that have been demonstrated to support the survival and function of dopaminergic neurons.

Participants will serve as their own donor for the tissue, which will be implanted at the time they undergo DBS surgery.

*Transplantation and Growth Factors:* The two main strategies aimed at preventing disease progression have been to either transplant cells or tissues in an attempt to replace the lost dopaminergic neurons or to deliver growth factors that can restore the injured neurons before they die. Clinical trials involving the transplantation of dopaminergic tissues into the brain have not been able to demonstrate clinical benefit (Olanow et al, 2003). Additionally, the source of the transplant material, fetal tissue, has raised considerable ethical issues regarding the viability of this therapeutic strategy (Hoffer and Oslon, 1991). On the other hand, studies involving the application of various growth factors to dopaminergic tissues have shown more promising results. Pre-clinical studies have identified several growth factors, including GDNF (Gash et al, 1996), BDNF (Tsukahara et al 1995), and CNTF (Clatterbuck et al, 1993), that are able to support the survival and maintenance of dopaminergic neurons. Additionally, pilot studies investigating the direct delivery of GDNF into the brains of patients with PD have shown safety as well as some clinical improvement (Slevin et al, 2005, Gill et al, 2003). Nevertheless, strategies utilizing growth factor delivery raise additional questions, such as which growth factors should be used and how should they be obtained, delivered, and dosed. Currently purified growth factors are very difficult to manufacture and access is limited by substantial patent restrictions. As a way to overcome these obstacles, this proposal is designed to investigate the use of an autologous source of cellular tissue from the peripheral nervous system (PNS) that has been shown to produce and express several important growth factors.

*Peripheral nerve tissue and Schwann Cells:* The predominant cell type in the PNS is the Schwann cell (SC). Under normal conditions, SCs support and maintain axonal function and metabolism. In response to injury, SCs upregulate the production of growth factors that play a major role in the repair of the damaged nerve. The growth factors produced include those that have been shown to promote and maintain dopaminergic neurons in experimental conditions: GDNF (Henderson et al, 1994), BDNF (Meyer et al, 1992) and NT-3 (Funakoshi et al, 1993). The central hypothesis of this proposal is that the harvesting of the peripheral nerve graft will initiate the production of growth factors through the injury response, and that the transplanted graft will allow the SCs to associate with the degenerating dopaminergic neurons and deliver the expressed growth factors to restore and maintain the injured neurons over time.

F1.0100

## Form B: Medical IRB Research Description

The primary objective of this pilot study is to demonstrate safety of the approach: introducing a minor modification of a standard, FDA approved neurosurgical procedure in use for over a decade to implant autologous peripheral nerve into the central nervous system. As such, the study is designed to pose minimal risk and minimal inconvenience to the subjects. Additionally, the test paradigm is performed strategically to not interfere with the surgery or delivery of the scheduled clinical DBS therapy. The scientific basis for this study is that the implanted peripheral nerve tissue is naturally well suited to provide multiple growth factors that have been shown experimentally to support the survival and function of dopaminergic neurons. **Central to this proposal is the hypothesis that the implanted tissue will physiologically deliver growth factors to restore to normal function the afflicted dopaminergic neurons found in PD.**

DBS for PD was approved for use in 2002 and has been shown to be an effective treatment for patients with advancing symptoms that are refractory to medication management (Follett et al, 2010). A recent study has also shown that DBS for PD is better than medical management alone for patients with advanced disease (Weaver et al, 2009). Nevertheless, any surgical procedure carries a risk of adverse events. Specific risks of DBS surgery include, intracranial hemorrhage, stroke, development of a new neurological deficit, and complications related to hardware malfunction. A retrospective study evaluating over 300 DBS procedures for movement disorders concluded that DBS is safe and effective, and that even though the overall reported incidence of adverse events is relatively high (43.3%), most are not serious, but are transient and do not pose a significant risk (Kenney et al 2007). The authors also reported the incidence of life threatening vascular adverse events as uncommon (1.6%). Thus, this pilot study will be performed in subjects who have already elected to undergo a safe procedure that has a known adverse event profile.

This study is innovative in several ways, including the clinical focus, the scientific basis, and the procedural approach.

First, the clinical focus of the project is directed toward the rescue and regeneration of damaged dopaminergic neurons. Most clinical studies of PD involve symptomatic treatments, but do not directly attack the underlying pathophysiology. In an attempt to reverse the pathologic process, peripheral nerve tissue will be implanted into the area of cell loss. Peripheral nerve tissue was selected because it has been shown to produce a host of growth factors that provide support for the dopaminergic neurons that are at risk for further degeneration.

Second, the project is novel scientifically in its approach to promote cell survival. While some studies using a single growth factor have shown modest clinical benefits on PD (Slevin et al, 2005, Gill et al, 2003), there are several problems with the approach. One problem is that the delivery is currently limited to a single growth factor. Another is that the delivery requires a chronically implanted device or gene therapy approach. Finally, the target for growth factor delivery is not necessarily in the region of the cell loss. This project has been designed specifically to overcome these issues. Peripheral nerve tissue is an ideal source for donor tissue. As stated previously, in response to nerve injury, peripheral nerve tissue increases its production of growth factors to initiate and maintain nerve repair. The SC is the main source for these growth factors, many of which support dopaminergic cell survival and function. It is likely that multiple factors will be better able to rescue and sustain the impaired neurons. Additionally, the autologous nerve tissue will be implanted directly into the SNpc, the anatomical region of the PD-injured dopaminergic cells. In this way, a natural source of growth factors will be delivered directly into a major area of cell damage.

Third, the project is novel in its methodological approach. The most significant feature of the protocol is the combined timing of the graft harvesting and implantation with the scheduled deep brain stimulation surgery. In this institution DBS surgery is routinely performed and is accomplished in two stages. Stage I is a preparatory surgery and is performed under general anesthesia. It includes the placement of the pulse generator, tunneling of the lead extensions, and the placement of the two frontal burr holes to be used as access for the microelectrode recording. It is during this surgery that the peripheral nerve graft will be prepared for harvesting from the sural nerve. This is accomplished

F1.0100

## Form B: Medical IRB Research Description

through a standard neurosurgical approach used for biopsy of the sural nerve and typically takes approximately 15 minutes. Stage II surgery is performed 5 days later and includes the placement of the DBS electrodes utilizing frame-based stereotactic guidance and microelectrode recordings to confirm targeting. The targeting and confirmation for the stimulating electrodes also confirms the targeting of the substantia nigra, the target of the peripheral nerve graft. The peripheral nerve graft will then be harvested and implanted into one substantia nigra *only after* both electrodes have been placed successfully. In this way, the study portion of the procedure does not interfere with the scheduled DBS surgery or treatment.

### **Overall, this study integrates several novel concepts based on clinical, scientific, and technical grounds.**

The concept of tissue transplantation into the CNS has been explored as a therapy for the treatment of multiple conditions, including PD (Freed et al, 2001) Multiple Sclerosis (Stangel 2004) and Spinal Cord Injury (Levi *et al.*, 2002). Several animal studies have demonstrated the feasibility of transplantation of various tissues into the CNS, including embryonic ventral mesencephalic cell suspensions (Brundin et al, 1986) and solid grafts (Strömberg et al, 2000, van Horne et al, 1991), adrenal medulla grafts and co-grafts (Watts et al, 1995), carotid body cell aggregates (Arjona et al, 2003), fetal cerebellar (Bankiewicz et al 1991) and amniotic tissue (Bankiewicz 1994), as well as purified Schwann cells (Pizzorusso et al, 1994).

Studies in both humans and animals have shown the safety of the transplantation of purified SCs into the brain and spinal cord (Pizzorusso *et al.*, 1994; Kohama *et al.*, 2001; Stangel, 2004; Saberi *et al.*, 2008). In the study by Strangel, autologous SCs were transplanted into lesions in the right frontal lobe of the brains of MS patients. While the treatment did not provide any significant clinical benefit in this trial, the transplantation was determined to be safe with “no complications and neither inflammation nor abnormal cell growth.” Additionally, Stangel notes that the benefit to an autologous transplantation of SCs is that each patient is able to serve as his/her own donor, minimizing the need for immunosuppression. This study will utilize grafts of peripheral nerve tissue, which contain SCs, rather than using isolated SC suspensions. This choice is based on the finding that continued contact between the SCs and the extracellular matrix (ECM) of the peripheral nerve tissues is very important for SC function. Chernousov et al (2008) have shown that laminin and collagen, proteins of the ECM, regulate SC function and survival and help to promote neurite outgrowth and cellular repair.

The safety of autologous peripheral nerve grafts into the CNS is supported by the results of investigations in both non-human primate models (Levi *et al.*, 2002) and in patients with PD (Watts *et al.*, 1997). Following positive results in a study examining the efficacy of intra-striatal co-grafts of autologous adrenal medulla and sural nerve in macaque models of PD (Watts *et al.*, 1995), the research team placed such co-grafts in the caudate and putamen of five human subjects with advanced PD (Watts *et al.*, 1997). The surgery proved to be without complications and was ultimately deemed both safe and successful. The safety of transplantation into the SNpc has been demonstrated by Mendez et al (2002) by placing cell suspensions bilaterally into the SN, as well as the putamen, without any perioperative or long term complications. To date, results from the first seven participants in our initial pilot study (IRB 12-1021-F6A) have only shown adverse events (Urinary retention, hypomania, superficial cellulitis, cough, and headache) in line with standard DBS surgeries. Therefore, evidence from the literature suggests that stereotactically grafting peripheral nerve tissue into the SNpc will also prove to be a safe procedure for PD patients.

An inquiry to the FDA regarding the need for permission or oversight yielded a response stating that the study does not meet criteria for the need for FDA approval or oversight based on the protocol design in which the patients donate their own tissue, the tissues are not modified or enhanced prior to implantation, and the implantation occurs during a procedure that the subjects have already elected to undergo for clinical reasons. A copy of this letter can be found at appendix A.

F1.0100

## Form B: Medical IRB Research Description

Data from this pilot proposal will be used to generate a programmatic investigation of this approach with respect to impact on symptoms, optimization of graft size and placement, and mechanism of action. If successful, this treatment strategy could significantly change the treatment of PD and could have an impact on other neurodegenerative disorders as well.

In summary, this pilot study will provide safety data that can be used to generate a larger phase III clinical trial. If successful, it would herald the development of a new treatment for PD in which patients are able to provide their own tissue as a source of growth factors that could arrest or reverse the ongoing cellular loss that is responsible for their devastating motor dysfunction.

**2. Objectives:** The first specific aim is to assess the feasibility and safety of the combined peripheral nerve graft/DBS surgical procedure. The second specific aim is to evaluate the long term clinical safety of the peripheral nerve implant.

**3. Study Design:** We are proposing the implantation of autologous peripheral nerve grafts into the SNpc of participants with PD undergoing deep brain stimulation (DBS) surgery. This approach is designed to test the safety of a new therapeutic strategy, in which Schwann cells (SC) within peripheral nerve grafts serve as a source of neurotrophic factors, which have been shown experimentally to support the survival and growth of the neurons that degenerate in PD.

This study will investigate a cellular treatment that could provide trophic support for diseased neurons and possibly halt or reverse the degeneration. We will evaluate the feasibility and safety of the procedure as well as the long term safety of the combined treatment. By design, participants will undergo the nerve graft preparation and implantation during the DBS surgery. Following a standard protocol, DBS surgery is performed by the PI in two stages: a preparatory stage I procedure, followed five days later by a second surgery (stage II) to implant the stimulating electrodes into the designated target. The peripheral nerve graft preparation and implantation is designed to impose minimal risk and discomfort to the participants and is performed during these two stages. The graft preparation is performed utilizing a standard neurosurgical approach used for sural nerve biopsies during the stage I DBS surgery, performed under general anesthesia. The harvesting and implantation of the nerve graft is performed during the stage II DBS surgery. Clinical evaluations for safety will begin directly following graft implantation and continued at regular postoperative time points while the participant is admitted as an inpatient. Participants also undergo a standard post-op CT or MRI scan that is used to verify electrode placement and check for the possibility of hemorrhage.

Participants will be followed closely clinically at regular time points for 24 months after implantation. They will be evaluated for possible neurological sequela through scheduled neurological exams, including use of a Unified Parkinson's Disease Rating Scale (UPDRS), during follow up appointments. Additional evaluations will occur during routine visits for DBS programming, adjustments, and optimization. Preoperatively and at the 24 month visit, formal neuropsychological and non-motor symptoms and quality of life exams will be administered. Participant adverse event profiles will be compared to those of routine DBS PD patients from our program as well as to the adverse event profiles reported in the literature for the same DBS procedure.

The anticipated outcome is that the procedure can be performed in a safe and efficient manner, adding not more than 30-45 minutes to the length of each stage of the DBS procedure. It is further anticipated that the grafts will prove to be clinically safe over the 24-month follow-up period with no greater adverse events compared to DBS procedures without graft placement. This study poses minimal risk as the additional procedures are "piggy-backed" to a major neurosurgical procedure that is routinely performed for patients with PD. If successful, this treatment approach would be widely available to any patient undergoing DBS surgery for PD with minimal risk and minimal cost.

**4. As a pilot project, the primary outcome is safety.** The peripheral nerve grafts will be implanted in patients with PD who are concurrently undergoing DBS surgery in the FDA-approved targets for PD, the subthalamic nucleus (STN) or the internal globus pallidus (GPi). Thus, only patients who have already been approved for bilateral DBS surgery will be eligible for this study. The peripheral nerve

F1.0100

## Form B: Medical IRB Research Description

graft will only be placed after all elements of the DBS system have been implanted. This not only eliminates the need for a separate surgery, but also ensures that the patient will receive the full benefits of DBS therapy regardless of the outcome of this safety trial.

**5. Study Population: Sixteen subjects** with a diagnosis of PD who have been selected and consented for DBS of the STN or GPi will be asked if they would like to participate in the study. In this way, the ability to participate in the study will not play a factor in the decision to undergo DBS therapy. Participants will be between 40 and 75 years of age and will include men, women, and minorities.

### Inclusion Criteria:

- Undergoing DBS of the STN or GPi
- Between the ages of 40-75
- Able to give informed consent
- Show a positive response to sinemet
- show no significant cognitive deficit per a formal neuropsychological exam,
- be able to tolerate the surgical procedure

### Exclusion Criteria:

- Any condition that would not make the subject a candidate for DBS of the STN or GPi
- Under the age of 40 or over the age of 75
- Unable to give informed consent
- Previous PD surgery or intracranial surgery

**6. Subject Recruitment Methods and Privacy:** Potential participants will be approached in the clinic setting after they have elected to undergo DBS surgery for PD. As participants will be recruited from patients who have elected to receive DBS therapy, refusal to participate in this study will not prevent them from getting their recommended and selected treatment for their PD symptoms. No advertising will be performed.

**7. Informed Consent Process:** Prior to entering the study, the risks and benefits of participating will be explained to the patient by a member of the study team authorized to obtain informed consent. Written informed consent from the patient will be placed in each patient's medical record and documentation of the informed consent process will be placed in the patient's progress notes. A signed informed consent form will be retained by the investigator. The study participant will receive a copy of the informed consent form. Only subjects with intact cognition and consent capacity will be allowed to participate.

**8. Research Procedures:** A Summary of Study Procedures can be found below. All tests and procedures listed below are being done for the purpose of the research study only. More detailed information about some of the procedures is shown below.

|  | Screening | SURGERY   |           | FOLLOW-UP                |            |             |             |             |
|--|-----------|-----------|-----------|--------------------------|------------|-------------|-------------|-------------|
|  |           | (Stage 1) | (Stage 2) | 24-48<br>hour<br>post op | Month<br>6 | Month<br>12 | Month<br>18 | Month<br>24 |
| Study Consent                          | X         |           |           |                          |            |             |             |             |
| Medical History                        | X         |           |           |                          |            |             |             |             |
| Medication<br>History                  | X         |           |           |                          | X          | X           | X           | X           |
| UPDRS                                  | X         |           |           |                          | X          | X           | X           | X           |
| PDQ-8                                  | X         |           |           |                          |            |             |             | X           |
| Non-motor<br>symptoms scale            | X         |           |           |                          |            |             |             | X           |
| Gait assessment                        | X         |           |           |                          | X          | X           | X           | X           |
| Exposure and Prep<br>of the peripheral |           | X         |           |                          |            |             |             |             |

PNG/PD  
Version 4  
Dated: 4 June 2014

F1.0100

**Form B: Medical IRB Research Description**

|  |   |   |   |   |   |   |   |   |
|--|---|---|---|---|---|---|---|---|
| Nerve  |   |   |   |   |   |   |   |   |
| Harvesting and implanting of the nerve graft |   |   | X |   |   |   |   |   |
| Protein analysis of peripheral nerve tissue  |   | X | X |   |   |   |   |   |
| Record DBS Settings                          |   |   |   |   | X | X | X | X |
| MRI  | X |   |   | X |   |   |   | X |
| Neuro-psych Evaluation                       | X |   |   |   |   |   |   | X |
| Adverse Event assessment                     | X | X | X | X | X | X | X | X |
| Videotaping                                  | X |   |   |   | X | X | X | X |

As part of the standard preoperative DBS protocol, subjects will be evaluated using the unified Parkinson's disease rating scale (UPDRS) and undergo a formal neuropsychological evaluation. Subjects will then be scheduled for their two stage DBS surgeries. Stage I surgery is preparatory, is performed under general anesthesia, and includes the placement of the pulse generator, tunneling of the lead extensions from the pulse generator pocket incision just below the collar bone to the scalp behind the ear, and the placement of the two frontal burr holes to be used as access for the microelectrode recording and stimulator placement performed during the second stage. It is during this surgery that a sural nerve graft will be prepared for harvesting for the second stage of the surgery. This is accomplished through a standard neurosurgical approach used for biopsy of the sural nerve. A 3-4 cm incision is made longitudinally just above and behind the lateral aspect of the ankle. The sural nerve lies in the subcutaneous space, is easily identified, and is then isolated and transected distally. A small silk suture is loosely placed around the proximal segment, 2 cm from the distal transaction. The suture serves as a marker for identification for harvesting during the second stage. Transecting the nerve initiates the injury response of growth factor production. Stage II surgery includes the placement of the DBS electrodes utilizing frame-based stereotactic guidance and microelectrode recordings to confirm targeting. The DBS electrodes will be placed according to standard clinical practice. The peripheral nerve grafts will then be harvested and implanted into one SNpc after both DBS electrodes have been placed successfully. For this component, the previously created incision in the ankle region is re-opened under local anesthesia, the marking stitch is identified, and the sural nerve is transected 2 cm proximal to the previous distal transaction. The nerve segment is then placed in normal sterile saline and trimmed for loading into the transplant cannula. The graft, ~0.8mm in diameter and ~1cm in length is then deposited stereotactically into the SNpc. All incisions are then closed in the standard, surgical, subcuticular fashion. In this way, the study portion of the procedure will not interfere with the scheduled DBS surgery or treatment.

Participants will then be followed by our clinical routine for their DBS treatment, including a normal postoperative one to two day hospital stay, a one and two week post-operative visit, and multiple neurological clinical visits for initial stimulation programming and optimization. A routine head CT or MRI scan will be obtained within 24 hours after the completion of the second surgery. Subjects will undergo formal UPDRS evaluations at 6, 12, 18, and 24 months and a repeat neuropsychological exam will be performed at 24 months. All adverse events will be reported and documented. Results will be compared to the known adverse event profile associated with bilateral DBS of the STN for PD as documented in the literature. The expectation is that the grafting of peripheral nerve tissue to the SNpc will have an adverse event profile that is no different than that of DBS surgery alone.

In this study, subjects will be monitored for both perioperative and long term postoperative adverse events. Clinical monitoring will be performed by the movement disorders neurosurgeon, neurologist, and the clinical study coordinator, a movement disorders neurology PAc experienced in DBS evaluation and programming. Pre-operative clinical baseline data will include a UPDRS evaluation, formal neuropsychological evaluation, a quality of life assessment (PDQ-8), non-motor symptom questionnaire, PNG/PD

Version 4  
Dated: 4 June 2014

F1.0100

## Form B: Medical IRB Research Description

gait assessment, and a co-morbidity profile obtained from the pre-operative medical history. The perioperative period is arbitrarily designated as the time from day of the first stage surgery to two weeks following the day of the second stage surgery. This allows for routine clinical assessments to take place during patient contact while in the hospital setting and during the routine two week post-operative visit. During this time period, adverse events will be recorded from clinical reporting and chart review as well as from specific queries by the clinical coordinator at the two week post-op visit. A routine post-operative scan, MRI or CT will be performed within 48 hours of the conclusion of the second stage of the surgery. Adverse events will be categorized as either related to PD, DBS surgery, or not related to either. In addition, adverse events will be categorized as mild, moderate, or severe, as defined by the Medical Dictionary for Regulatory Activities, version 11.0. Serious adverse events will be designated as any event that results in death, disability, or prolonged or new hospitalization or that is life threatening or that requires medical or surgical intervention.

Postoperative data will be collected at 6, 12, 18, and 24 months from the time of the second stage surgery. Data collection will take place during scheduled clinic visits and will include UPDRS scores, medication dosages, recording of DBS settings and programming changes, gait analysis, as well as a query of adverse events dating from the last clinical visit. At the 24 month visit, the formal neuropsychological non-motor symptom, and the PDQ-8 exams will be repeated. As a pilot safety study, the participant adverse event profile, quality of life scores, and neuropsychological evaluations will be compared to those reported in the literature. Additionally, subject scores on the UPDRS parts III and part IV (motor and complications off therapy) and medication modifications will be evaluated for possible clinical benefit from graft placement. Off medication assessments will be performed at least three hours but possibly as much as twelve hours off medication (time from last PD medication dose). This time frame has been deemed acceptable by the IRB at this institution in a previous study involving participant assessment off PD medications (Slevin et al, 2005).

We will request permission from all subjects to videotape them at screening and then post-operatively, at follow-up visits. Subjects may be videotaped during examinations in order to visually document changes in their exams over time.

We will also ask the subjects if they agree to be contacted in the future with regards to their willingness to participate in additional follow up visits or in future research studies about how to prevent, detect or treat Parkinson's disease.

### POTENTIAL FUTURE USE

#### Banking of tissue specimens

A small sample (approximately ½ inch) of the peripheral nerve obtained during the first and second stages of the DBS surgery will be frozen and kept at the University of Kentucky under the direction of Dr. Craig van Horne for research purposes. The nerve tissue collected will not be needed for the diagnosis or management of the participant's health and will not interfere with the graft that will be implanted during the main part of the study. The results of any testing done on the samples will not be shared with the participant.

No additional tissue will be taken. If participants agree, the sample obtained for this research study may be tested immediately or may be frozen and examined later. Donated samples may be tested for markers that might indicate how the nerve graft is working. No genetic testing will be performed on collected samples.

Samples will be kept until we receive written notice from the participant that they wish to have their sample destroyed. Subjects will be advised that destruction of their sample may not be possible because the sample may no longer exist. Participation in this part of the study is optional. Participants can refuse to take part in the banking of their peripheral nerve and still take part in the main study.

F1.0100

## Form B: Medical IRB Research Description

**9. Resources:** The research procedures will be carried out at the UK Chandler Medical Center, and the Kentucky Neuroscience Institute. The patients will be followed by Doctors van Horne and Slevin and their research team which includes physicians and certified nurses and clinical research coordinators during the study. Emergency medical equipment, medications and supplies will be at the physician's disposal should the patient have an acute untoward reaction. The UK Center for Translational Science will provide Quality Assurance monitoring throughout the life of this study.

**10. Potential Risks:** The most significant health risk of this study is related to the surgical procedure at the time of graft placement. The overall risk of a major adverse event (considered to be catastrophic hemorrhage) of graft placement is assumed to be no greater than that of a single needle pass through the brain, reported to be approximately one in 500 or 0.2% (Kenny et al, 2007). Additional risks are associated with the graft harvesting procedures. The surgical risk is minimal and this part of the protocol is considered a minor surgery and employs a surgical approach that is used for sural nerve biopsies. Discomfort is minimized by performing the initial portion of the procedure under general anesthesia. The incision is ~3cm in length located above and behind the lateral aspect of the ankle.

The sural nerve is a sensory nerve that supplies sensation to the lateral aspect of foot and heel. Typically, only one fascicle of the nerve is removed which usually causes no detectible sensory deficit. Larger biopsies have reported to lead to either temporary sensory loss or permanent loss of sensation to a small dermatomal patch on the outer aspect of the foot and/or heel.

Additionally, the grafting procedure has been designed to occur at the time of DBS surgery – so as not to require a separate surgery. The timing of the grafting procedure is scheduled to take place after the DBS electrodes have been placed so as to not interfere with the implantation and installment of the DBS electrodes. There could be a technical difficulty during the portion of the procedure that involves graft harvesting or implantation that would prevent adequate graft placement. Thus, if there is a problem with graft harvesting or placement, participants will still receive their elected DBS therapy but would not receive the graft.

Although this study does involve grafting, participants will donate their own tissue. This eliminates the risk of graft rejection and obviates the need for immunosuppressant medications typically used with other transplant studies.

**Release of videotaped neurological session:** In order to maintain the scientific and educational integrity of the videotaped sessions we are unable to blur out the subject's entire body. We will however, blur out their eyes and nose which will only allow the viewer to see their mouth. The risks associated with allowing the release/showing of the subjects' videotaped sessions include full body and mouth recognition by the viewer.

Subjects will be provided with the option of whether or not to allow the release of their videotaped sessions. Their election will be documented in the signed informed consent.

**11. Safety Precautions:** Provisions to guard against the potential risks and discomforts discussed in section 9 are as follows: Every precaution to prevent a direct study injury will be taken by medical personnel and the investigators. The research subject will be followed by physicians, fellows, registered nurses and other research staff members for the duration of the subjects' hospitalization. Routine care will be provided by the hospital staff. Emergency medical equipment, medications and supplies will be at the physician's disposal should the subjects have an acute untoward reaction. The subjects will be monitored for clinical adverse experiences throughout study therapy. Throughout the study, all adverse events will be monitored and recorded. The UK Center for Translational Science will provide Quality Assurance monitoring throughout the life of this study

**12. Benefit vs. Risk:** As the scientific basis of this study to restore the degenerating dopaminergic neurons associated with PD, the potential benefit would be an improvement in the participant's symptoms due to graft function. This would benefit the participant by reducing the amount of therapy

F1.0100

## Form B: Medical IRB Research Description

(medication and or stimulation) needed for symptom control. In the long term, participants could also experience a stabilization of the progression of their disease.

**13. Available Alternative Treatment(s):** Should a subject decline the opportunity for participation in the study they will continue on with their DBS surgery, and FDA approved treatment for medically refractory PD. There are no other current combined treatment options that incorporate DBS. Please note that DBS therapy includes continued medical therapy to optimize the treatment of PD symptoms.

**13. Research Materials, Records, and Privacy:** The investigative team maintains the right to keep, preserve, use and dispose of the findings of this investigation in accordance with University of Kentucky Records Management and IRB policies and guidelines. Investigational records from this study will be maintained in a confidential manner; subject names will not be associated with any published results. All clinical information obtained will be considered to be part of the patient's medical chart and will be treated as such according to standard HIPAA guidelines and regulations. Additionally, clinical information relating to the study will be copied, de-identified, coded, and placed in a separate binder. Binders will be kept in a locked cabinet in the office of the study coordinator.

**14. Confidentiality:** We will keep private all research records that identify the subject to the extent allowed by law. We will make every effort to prevent anyone who is not on the research team from knowing that the subject gave us information, or what that information is.

Subject information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. The subject will not be personally identified in these written materials. We may publish the results of this study; however, we will keep subject name and other identifying information private.

Videos taken of a subject during study related neurological testing sessions may be shown at local and national meetings, conventions, conferences for scientific and educational purposes only. Release of the subjects' videos will not be made if the subject has not authorized it.

In order to process the subjects study payments we will need to collect their social security number. The subject does not have to give us this number however, refusing to provide us with their social security number may result in their not receiving study payment. The subject can refuse to provide their social security and still be enrolled into the study.

The study information collected from the subjects participation in the study will be collected and stored in paper charts and video. They follow the principles of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Subject charts, video, and any other items containing confidential items will be stored in a safe place overnight and not left on the desk. Charts will not be left in an area where others might have access to them.

The subject should know, however, that there are some circumstances in which their information may have to be shown to other people. For example, the law may require us to show their information to a court.

Officials from the Food and Drug Administration (FDA) and the University of Kentucky may look at or copy pertinent portions of records that identify the subject.

**15. Payment:** Subjects will be compensated for time and travel. They may receive up to \$500.00 for taking part in this study. Subjects will receive \$100.00 compensation following study visits at the 6, 12, 18, and 24 month visits.

F1.0100

**Form B: Medical IRB Research Description**

**16. Costs to Subjects:** The subject and/or their insurance company, Medicare or Medicaid will be responsible for the costs of all care and treatment they receive during this study that they would normally receive for your condition. These are costs that are considered medically reasonable and necessary and will be part of the care they receive if they do not take part in this study. Subjects will be responsible for all costs associated with their DBS surgery.

There will be no charge to the subject for their participation in this study. The study-related procedures, and study visits will be provided at no charge to the subject or their insurance company.

Costs associated with treating any injury suffered while participating in this study will be the responsibility of the subject or their insurer. Subjects will be advised to ask their insurer if they have any questions regarding their insurer's willingness to pay these costs; this includes contacting Medicare or Medicaid if they are covered by Medicare, or Medicaid.

A co-payment/deductible may be required by their insurer or Medicare/Medicaid even if the insurer or Medicare/Medicaid has agreed to pay the costs. The amount of this co-payment/deductible may be substantial.

Subjects do not give up their legal rights by signing this form.

**17. Data and Safety Monitoring:** Monitoring for adverse events will be conducted in real-time by the study investigators and study coordinators. Risks involved with this study are considered greater than minimal risk. For this reason, we will utilize the standing independent Data Safety Monitoring Board (DSMB) as chartered by the University of Kentucky Center for Clinical and Translations Science (CCTS) to monitor the safety of this study. The DSMB will meet semiannually or as needed, and will review subject recruitment, AE's, side effects, laboratory results, dropouts, protocol violations, and inclusion/exclusion criteria. More frequent meetings will take place if side effects or other problems are prevalent.

**18. Subject Complaints:** Subjects will be encouraged to address any complaint to any member of the study team including the PI. They will be told that they can, at any time, call the Office of Research Integrity at the University of Kentucky at (859) 257-9428 or toll free at 1-866-400-9428.

**19. Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture:**  
N/A

**20. HIV/AIDS Research:** N/A

**21. PI-Sponsored FDA-Regulated Research:** N/A. This study is exempt from IND and FDA monitoring.