Project Title: Remote Mobile Decision Support System for Nurse Management of Neuromodulation Therapy Phase II

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Summary

The objective of this application is to prospectively test the use of a mobile deep brain stimulation (DBS) clinical decision support tool in postoperative clinical care. The central hypothesis is that the use of a mobile DBS clinical decision support tool for individual patient management will enable a non-expert DBS programmer to manage a patient's DBS therapy by using a combination of visits to the patient's home and telemedicine. This hypothesis was formulated from pilot studies done at the Medical College of Wisconsin that showed dramatic decreases in DBS programming time compared to standard care for clinicians who used an iPad-based mobile DBS clinical decision support tool (greater than 80% time savings). We are currently conducting Phase I of this study, in which we are prospectively evaluating a mobile DBS clinical decision support tool to aid expert DBS programmers. The rationale for the proposed research is that by integrating information already collected from patients, computational models, clinical informatics, and mobile computing devices, a non-expert can manage DBS patients.

Background

Computational modeling of DBS has been shown to be a useful way to predict the effects of DBS in individual patients (Butson, Cooper, Henderson, & McIntyre, 2007). This technique uses pre- and post-operative imaging to construct detailed, patient-specific models that predict the electric field and volume of tissue activated (VTA) for each set of stimulation parameters (active DBS contact(s), voltage, pulse width, frequency) (Butson, Maks, & McIntyre, 2006; Butson & McIntyre, 2005, 2006, 2008). The VTA represents the extent of activation of neural tissue based on the assumption that the local stimulation targets are large myelinated axons (McIntyre,Grill, Sherman, & Thakor, 2004; McIntyre, Richardson, & Grill, 2002). These model predictions have been validated in both primate and human studies (Butson et al., 2007; Miocinovic et al., 2009), and the utility of these models has begun to change the approach to DBS programming (Butson, Tamm, Jain, Fogal, & Krueger, 2012; Frankemolle et al., 2010). It has been demonstrated that by

doing retrospective analysis on prior DBS patients, probabilistic maps of stimulation can be generated (Butson et al., 2011).

The second component is a platform that facilitates the delivery and use of these models in a clinical setting. In a recent study with our collaborators we developed ImageVis3D Mobile, an app that provides volume and geometry rendering capabilities on iOS devices (iPhone and iPad) and that builds on the volume rendering system library Tuvok (Fogal & Krueger, 2010). In a collaboration with Dr. Butson, ImageVis3D Mobile was recently adapted to incorporate computational models of DBS, and to provide an interface that is amenable to a clinical workflow in an iPad app (Butson et al., 2012).

We can therefore integrate computational models, probabilistic maps of stimulation, and a iPad application to create a mobile DBS clinical decision support tool that can aid non-experts in the DBS programming process.

Specific Aims

Our central hypothesis is that the use of a mobile DBS clinical decision support tool for individual patient management will enable a non-expert home health nurse to manage the care of a DBS patient. This hypothesis was formulated from pilot studies that showed the efficacy of the mobile DBS clinical support system in aiding expert programmers.
We will prospectively test the use of a mobile DBS clinical decision support tool in postoperative clinical care in the patients' homes. The *rationale* for the proposed research is that computational models, clinical informatics, and mobile computing devices can be used to enhance non-expert programmers. This hypothesis will be tested in *one specific aim*: 1) Measure effectiveness of our mobile DBS clinical decision support tool in aiding home health nurses to manage DBS patients in their homes.

The primary outcome for Phase II of this study is number of clinic visits for patients during the first 6 months of DBS therapy. For the secondary analysis, we will test for differences in PDQ-39 scores between the two groups.

Research Plan Phase II

Enrollment

A total of 260Parkinson's disease patients and their caregivers will be needed in order to complete the study at the University of Florida during Phase II. Specifically, 130 Parkinson's patients in the standard of care cohort (65 patients/65 caregivers) and 130 Parkinson's patients in the intervention cohort (65 patients/65 caregivers. We anticipate approximately 10 subjects will withdraw. Participants are not required to have a caregiver in order to participate in the study.

Patients included in the study will meet all of the following Inclusion criteria

- Age 30-80
- Planning to receive a DBS device from University of Florida Health as part of standard of care for Parkinson's disease, or already have a DBS device implanted by University of Florida Health, but have not yet received DBS

programming
- Participants must live in Florida and within 250 miles of the study site.
- Patients must be fluent English-speakers

Patients will be excluded from the study if

- Their DBS programming will be conducted by a different other Institution than University of Florida Health
- They have received prior DBS programming
- They expect to receive an additional DBS lead within 6 months of their initial DBS programming session, with the exception of patients initially approved for rapid staged or simultaneous bilateral implantation

Study Procedures

Patients will be enrolled either before or after DBS surgery. Patients must be enrolled prior to the first session for DBS programming. Patients will be recruited from the UF Center for Movement Disorders Clinic. Patients will be approached after their DBS Fast Track appointment prior to their DBS Surgery or after their DBS Surgery at their postoperative appointment. The Principal Investigator will identify potential participants in clinic or prior review of the clinic schedule to identify postoperative patients. The Principal Investigator will discuss the protocol with the patient and their caregiver/spouse. The patient will be consented before any protocol related procedures or collection of data commences and documented with a consent note in the source. Participants will be consented in a private clinic room.

Randomization

Following the DBS operation (lead implantation), patients will be randomized 1:1 to routine clinical programming (65subjects and 65) or to clinical programming assisted by the mobile DBS clinical decision support tool (65 subjects and 65 caregivers). Randomization will be stratified to control for expected variability resulting from different programming nurses, unilateral vs bilateral lead placement and miles (</>100 miles from site).

Standard clinical care arm

Subjects assigned to the standard clinical care arm will undergo routine clinical programming.

Mobile Decision Support arm

The patient's MRI and CT scans will be used to generate models for the mobile DBS clinical decision support tool.

The DBS programming clinician will use ImageVis3D Mobile app on the iPad to program the DBS system. There is no patent for this app that is available on the Apple App Store. The local study team will de-identify MRI and CT images via Visage and a second user will validate the images are de-identified before sending them to Utah. A patient study code will be assigned by the local study team. The images will be

transferred to the University of Utah, where a patient specific computational model will be generated. The models will be transferred back to the clinician's iPad for use. The patients will be assessed according to the standard clinic schedule for routine care.

Patients in the intervention arm will be seen in the clinic at baseline (DBS battery placement preoperative appointment) and month 6. Patients will be visited in their homes at month 1 (device activation) and month 3. The patient will have month 2,4, and 5 visits either over the phone or a video call.

For visits in the patient's home, the nurse will bring the clinical DBS programmer with them to conduct programming. The nurse will leave the patient with multiple DBS settings that they can access via the patient programmer. For the visits that are conducted via phone/video, the nurse will direct the patient to make changes with their patient programmer. After the phone/video call visits, we will ask patients and their caregivers to fill out a short survey asking about the their satisfaction with the virtual visit (Provider Virtual Visit Survey and Virtual Visit Survey). The nurse will be aided by the mobile DBS clinical decision support tool during all DBS programming. At any point if the patient feels that they need additional in home visits, or need to visit an expert in the clinic, they can schedule an appointment.

Both Clinical and Intervention Arms

Programming sessions will be conducted during the month 1,2,3,4 and 5 visits. Programming adjustments may also occur at month 6 if needed, but will occur after study procedures are finished.

We will measure the time spent on DBS programming for patients in each group. We will capture total time spent on DBS programming as well as number of programming sessions. We will compare total time spent programming for the standard care versus the intervention group for each session over 6 months. We will also capture the DBS settings that are selected for the patient during each visit.

Neurological Evaluation

Patients will be assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) at baseline, month 3 and month 6 (off medication). This assessment may be videotaped in order to facilitate independent review of the rating assessment. If a participant chooses not to be video recorded, or video recording is not available at the site, an independent, clinically trained rater may conduct the assessment in real time.

Patient-Reported Outcomes

We will capture patient-reported quality of life (QOL) using the PDQ-39. The PDQ-39 is a validated, and a widely used scale completed by the patient, and is used to assess health-related quality of life in patients with Parkinson's disease. ~~and DBS~~. Patients will fill out rating scales using a web-based form on an iPad, over the phone or video call, or on paper before designated programming sessions. We will collect PDQ-39 at baseline, month 3, and month 6.

We will collect the Multidimensional Caregiver Strain Index (MCSI) at baseline, month 3 and month 6. The caregiver will report on the financial and time burden of the clinical visit. If the patient does not have a consented caregiver, we will collect this information from the patient. It is acceptable for either the patient or the caregiver to complete the survey, but it is preferable that the same person fill it out each time. Additionally along with the MCSI we will collect an accompanying questionnaire called the Patient Assessment of Care in Chronic Illness which will help us to interpret the MCSI.

Schedule of Assessments –Mobile Decision Support

NAME or Short Description of Item, Service, Activity	**Screening (Fast Track up to IPG Implant**	**Baseline (Preoperative IPG appointment)**	**(Month 1 post-op) *home***	**Month 2 (30+/- 7 days from baseline) *phone/video***	**Month 3 (60+/- 7 days from baseline) *home***	**Month 4 (90+/- 7 days from baseline) *phone/video***	**Month 5 (120+/- 7 days from baseline) *phone/video***	**Month 6 (150+/- 7 days from baseline)**
Informed Consent	**x**							
Medical History (including past UPDRS scores)	**x**	**x**						
Demographics	**x**	**x**						
Preparation of Decision Support System (depending on patient condition)		**x**						
Randomization	**x**	**x**						
All UPDRS III scoring by Blinded Rater	**x**				**x**			**x**
UPDRS III On Medication/On Stimulation								**x**
UPDRS III Off Medication/On Stimulation (videotaped)	**x (no stimulation)**				**x**			**x**
UPDRS I, II, and IV		**x**			**x**			**x**
PDQ-39 and visit burden report	**x***	**x***			**x**			**x**
DBS Programming Session (record settings and time spent programming)			**x**	**x**	**x**	**x**	**x**	
Caregiver MCSI and report of time spent caregiving (if applicable)		**x**			**x**			**x**
Patient Assessment of Care in Chronic Illness		**x**			**x**			**x**
Telemedicine Visit Satisfaction Survey (intervention arm only)				**x**		**x**	**x**	
Adverse Event and Concomitant Medication recording	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

***If PDQ was performed as part of SOC within 3 month of the IPG implant, it will be obtained during screening from the EMR. If not, it will be performed at Baseline visit.

Schedule of Assessments – Clinical Arm

NAME or Short Description of Item, Service, Activity	Screening (Fast Track up to IPG Implant	Baseline (Preoperative IPG appointment)	(Month 1 post-op)	Month 2 (30+/- 7 days from baseline)	Month 3 (60+/- 7 days from baseline)	Month 4 (90+/- 7 days from baseline)	Month 5 (120+/- 7 days from baseline)	Month 6 (150+/- 7 days from baseline)
Informed Consent	x							
Medical History (including past UPDRS scores)	x	x						
Demographics	x	x						
Preparation of Decision Support System (depending on patient condition)		x						
Randomization	x							
All UPDRS III scoring by Blinded Rater		x						x
UPDRS III On Medication/On Stimulation								x
UPDRS III Off Medication/On Stimulation (videotaped)	x (no stimulation)				x			x
UPDRS I, II, and IV		x			x			x
PDQ-39 and visit burden report (repeat if not done within 3 months of IPG)		x			x			x
DBS Programming Session (record settings and time spent programming)			x	x	x	x	x	
Caregiver MCSI and report of time spent caregiving (if applicable)		x			x			x
Adverse Event and Concomitant Medication recording			x	x	x	x	x	x

Programming IPads with Decision Support Software will be locked in a room here at the Center for Movement Disorders. Confidential computer-based files will only be made available to personnel involved in the study through the use of access privileges, passwords and encryption. Passwords and encryption are used to ensure that the electronic data is secure and housed in a locked room. Paper based files will be stored in a locked cabinet in a research room in the Center for Movement Disorders. This room is locked and only accessible to research personnel. Videos will be downloaded onto a password protected computer and stored on a restricted drive. The videos will only be accessed by a research personnel and will be destroyed at the end of the study.

Possible Benefits:

Participants and caregivers may or may not personally benefit from participating in this study. There is the possibility ~~for~~ that the patient may have to make fewer visits to the clinic for their DBS therapy to be managed.

The information obtained from this study may help improve the treatment of Parkinson's disease and DBS patients in the future.

Possible Discomforts and Risks:

The risks associated with this study will be explained to all participants, they will be shared in writing for the subject to review prior to participation. Expected outcomes from the stimulation patterns include the following side effects (e.g. feeling of tightness or pulling, sensory changes (reported as heaviness, numbness or tingling) or visual changes. These symptoms typically occur as part of standard clinic programming visits and are stimulation-induced, often transient and can be stopped immediately by turning the device off or to a lower setting as well as by returning the device to its normal home settings. For home visits, the home nurse will be with the subjects throughout the study to assess side effects. Should the subjects experience a side effect that is intolerable, the nurse will immediately stop the stimulation and turn the device off or turn it to the regular home setting. This is the same procedure that happens in clinic as part of standard of care. The nurse will then contact the PI or Co-investigators for further instruction. Any adverse events will be reported to the local UF IRB-01 according to reporting requirements.

Safety Monitoring and Reporting

Participants in both groups will be monitored for adverse events at each programming visit, and reportable events will be relayed to the lead clinical PI, Dr. Okun and the IRB. During a remote or home programming session, should the participant feel any discomfort or experience an adverse side effect, programming will be stopped immediately and the nurse will call the PI or Co-investigators.

This study will have a designated **Data Safety Monitoring Board (DSMB)** composed of five members (three neurologist, a statistician, and a non-neurological physician) without any ties to the current study or conflict of interest. The safety experience will be reviewed approximately every 6 months by the DSMB via email or telephone. This will start when the first patient is enrolled and end when the last patient completes the primary outcome. The DSMB will be informed of all serious adverse events and all mild adverse events which are potentially related to programming. The DSMB will designate each AE as mild or severe; as related, uncertain to be related or not related; and as anticipated or unanticipated. The DSMB has the authority to suspend further enrollment pending investigation of safety concerns raised by SAEs occurring in the trial.

Data Sharing and Storage

Images are transferred to and stored in the University of Utah Protected Environment, which is specifically approved to store identified human data. Images can be transferred in one of two ways:

1. PowerShare using under the existing agreement with University of Utah and University of Florida.
2. Secure File Transfer Protocol (sftp) in combination with two factor authentication using Duo.

All data captured for the study will be de-identified using unique study IDs and be stored using REDCap at the University of Utah. Research personnel will be assigned a username and password specific to the study in REDCap. No PHI will be transmitted to or stored on the iPad.

Analysis Plan

The primary outcome, number of clinic visits, will be evaluated we will use a Wilcoxon-Mann-Whitney test. With projected enrollment we will have 80% power to detect a difference between the control and experimental groups. For the secondary analysis, PDQ-39 scores will be aggregated into a time-weighted average score using a trapezoid-rule based area under the curve (AUC) calculation. This estimate of the overall QOL over the 6 month follow-up period will be compared using randomized block ANCOVA adjusting for the baseline PDQ-39 score. Finally, for a tertiary analysis, 6-month PDQ-39 overall and subscale scores, and UPDRS scores will be compared using the same method.

Patient Withdrawals

A participant may be removed from the study at the investigator's discretion. Subjects who withdraw or are withdrawn prematurely from the study will not be replaced.

Discontinuation of Study

The study may be discontinued at any time for any reason by the NIH, IRB or Lead Investigator prior to the completion of enrollment and follow-up for all participants.

Study Costs and Payments

Participants will not be charged or paid to participate in this study.

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