Human Subjects Protocol (HSP)

Form Version: June 25, 2015

- **You are applying** for IRB review of the research described in this form.
- **To avoid delay**, respond to all items in order and include all required approvals and documents.
- **To complete the form**, click the underlined areas and type or paste in your text; double-click checkboxes to check/uncheck. For more tips, see www.uab.edu/irb/forms .
- **Mail or deliver all materials to AB 470**, 701 20th Street South, Birmingham, AL 35294-0104.

Indicate the type of review you are applying for:

☒ Convened (Full) IRB *or*

☐ Expedited—See the Expedited Category Review Sheet, and indicate the category(ies) here: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

1. IRB Protocol Title: Noninvasive biomarkers to advance emerging DBS electrode technologies in Parkinson's disease.

2. Investigator, Contacts, Supervisors

a. Name of Principal Investigator: Harrison C. Walker
Degree(s)/Title: MD/Assistant Professor BlazerID: hcwalker
Dept/Div: Neurology/Movement Disorders Mailing Address: SC 360 UAB ZIP: 0017
Phone: 4-0683 Fax: 6-4039 E-mail: hcwalker@uab.edu

b. Name of Contact Person: Jennifer Mahaffey Title: Program Manager II Phone: 6-4030
E-mail: jmahaffe@uab.edu Fax: 6-4039
Mailing Address (if different from that of PI, above): SC 350D, Zip 0017

INVESTIGATOR ASSURANCE STATEMENT & SIGNATURE

By my signature as Principal Investigator, I acknowledge my responsibilities for this Human Subjects Protocol, including:

- Certifying that I and any Co-Investigators or Other Investigators comply with reporting requirements of the UAB Conflict of Interest Review Board;
- Certifying that the information, data, and/or specimens collected for the research will be used, disclosed and maintained in accordance with this protocol and UAB policies;
- Following this protocol without modification unless (a) the IRB has approved changes prior to implementation or (b) it is necessary to eliminate an apparent, immediate hazard to a participant(s);
- Verifying that all key personnel listed in the protocol and persons obtaining informed consent have completed initial IRB training and will complete continuing IRB training as required;
- Verifying that all personnel are licensed/credentialed for the procedures they will be performing, if applicable;
- Certifying that I and all key personnel have read the *UAB Policy/Procedure to Ensure Prompt Reporting of Unanticipated Problems Involving Risks to Subjects or Others to the IRB, Institutional Officials, and Regulatory Agencies* and understand the procedures for reporting;
- Applying for continuing review of the protocol at least annually unless directed by the IRB to apply more frequently;
- Conducting the protocol as represented here and in compliance with IRB determinations and all applicable local, state, and federal law and regulations; providing the IRB with all information necessary to review the protocol; refraining from protocol activities until receipt of initial and continuing formal IRB approval.

Signature of Investigator: _____ **Date:** 8/14/17

3. Protocol Personnel

Including the PI, list all key personnel (each individual involved in the design and conduct of this protocol including recruitment, informed consent, analysis of the data, and reporting of the results). Complete either the UAB (3.a.) or non-UAB (3.b) table, as applicable. Use the checkboxes to show each person's role, whether the investigator has financial interests as defined by the UAB CIRB, and briefly describe the individual's responsibilities for the research and qualifications to perform those responsibilities. Insert additional rows as needed.

FDA: For studies involving investigational drugs, list all investigators who will be listed on FDA Form 1572 and include a copy of the 1572. Send the IRB a copy of Form 1572 any time you update the form with the FDA.

a. UAB Personnel

Name	Blazer ID	Role	Financial Interest? *	Protocol Responsibilities and Qualifications
Harrison Walker	hcwalker	Principal Investigator	☒ No ☐ Yes	MD / Assistant Professor – Neurology Project conception, oversight of all aspects of project, consent privileges, clinical assessments, data acquisition, data analysis, interpretation of findings, publication of results
Barton Guthrie	guthrie1	☒Sub-Invest ☐Other	☒ No ☐ Yes	MD / Professor – Neurosurgery Consent privileges, neurosurgical procedures, interpretation of findings, publication of results
Arie Nakhmani	anry	☒Sub-Invest ☐Other	☒ No ☐ Yes	PhD / Assistant Professor - Electrical Engineering Software and hardware development, data analysis, interpretation of findings, publication of results
Christopher Hurt	cphurt	☒Sub-Invest ☐Other	☒ No ☐ Yes	PhD / Assistant Professor – Physical Therapy Data acquisition, data analysis, interpretation of findings, publication of results
Daniel Phillips	dphill	☒Sub-Invest ☐Other	☒ No ☐ Yes	EdD / Instructor – Speech Pathology (Otolaryngology) Data acquisition, data analysis, interpretation of findings, publication of results
Roy Martin	rmartin	☒Sub-Invest ☐Other	☒ No ☐ Yes	PhD / Associate Professor – Neurology Data acquisition, data analysis, interpretation of findings, publication of results
Gary Cutter	cutterg	☒Sub-Invest ☐Other	☒ No ☐ Yes	PhD / Professor – Biostatistics Statistical analyses, interpretation of findings, publication of results
Mark Bolding	mbolding	☒Sub-Invest ☐Other	☒ No ☐ Yes	PhD / Assistant Professor – Radiology Data acquisition, data analysis, interpretation of findings, publication of results
Anthony Nicholas	nicholas	☐Sub-Invest ☒Other	☒ No ☐ Yes	MD / Professor – Neurology Data analysis, interpretation of findings
Zachary Irvin	irwinz	☐Sub-Invest ☒Other	☒ No ☐ Yes	PhD / Postdoctoral Fellow – Neurology Data acquisition, data analysis, interpretation of findings, publication of results
Christopher Gonzalez	clg17	☐Sub-Invest ☒Other	☒ No ☐ Yes	MS / Research Assistant – Neurology Consent privileges, data acquisition, data analysis, interpretation of findings, publication of results
Daniel Kuhman	dkuhman	☐Sub-Invest ☒Other	☒ No ☐ Yes	MS / Research Specialist – Physical Therapy Data Acquisition, data analysis, interpretation of findings, publication of results
Mohammad Awad	mawad90	☐Sub-Invest ☒Other	☒ No ☐ Yes	MS / Graduate student - Electrical Engineering

				Software and hardware development, data analysis
Melissa Wade	tbicurn	☐Sub-Invest ☒Other	☒ No ☐ Yes	CRNP / Certified Registered Nurse Practitioner – Neurology Clinical management, device programming, consent privileges
Tesia Pair	tesia	☐Sub-Invest ☒Other	☒ No ☐ Yes	BS / Study Coordinator – Neurology Consent privileges, patient scheduling
Margaret Ashlie Cassidy	mam0908	☐Sub-Invest ☒Other	☒ No ☐ Yes	RN / Clinical Care Coordinator – Neurology Consent privileges, data acquisition
Julie Boyd	jmboyd2	☐Sub-Invest ☒Other	☒ No ☐ Yes	PA / Physician Assistant - Neurosurgery Consent privileges

*** Financial Interest** – for each investigator listed above, answer **Yes** or **No** as to whether the investigator or an immediate family member has any of the following:

- An ownership interest, stock options, or other equity interest related to the investigator's institutional responsibilities of any value.
- Compensation greater than $5,000 in the previous two years when aggregated for the immediate family
- Proprietary interest including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- Board of executive relationship, regardless of compensation.
- Any other Financial Interest as defined by the UAB CIRB.

If the investigator has a Financial Interest, a disclosure has to be made to the UAB CIRB. A completed CIRB evaluation has to be available before the IRB will complete its review.

b. Non-UAB Personnel - Include individuals who will interact or intervene with participants, obtain consent, or have access to private, identifiable information for research purposes.

Name	Title	Do the Non-UAB personnel have their own IRB approval?	Financial Interest? *	Protocol Responsibilities and Qualifications
Name: Institution:	☐ Sub-Investigator ☐ Other	☐ No - UAB IRB will determine if they are engaged in research. ☐ Yes - attach IRB approval	☐ No ☐ Yes	

c. Do the investigators listed above include any students using this research for their thesis or dissertation?

☐ No, continue with Item 3.d.
☒ Yes, complete the following

Student Name	Thesis/Dissertation Title
Neurology graduate student 1 (TBD) Neurology graduate student 2 (TBD) Physical Therapy graduate student (TBD)	The proposal budget covers these students, to be named. They will be incorporated into the protocol once it is active.

d. Is the principal investigator a student, fellow, or resident? ☐Yes ☒No

If Yes, complete items below and obtain signature of faculty advisor or supervisor:

Supervisor's Name: _____
Degree(s) / Job Title: _____
Additional Qualifications pertinent to the study: _____
Telephone: _____
E-Mail: _____
Signature: _____

e. Describe the principal investigator's activities related to this protocol and provisions made by the PI to devote sufficient time to conduct the protocol:

The Principal Investigator (PI) will provide oversight and guidance on conduct of clinical trial. The PI will designate responsibilities to study personnel. The PI has sufficient time and effort available to allow a successful management of this study.

f. Is medical supervision required for this research? ☒Yes ☐No

If Yes, who will provide the supervision?

☒ PI will provide -*OR*- Name:_____ Telephone:_____

If other than PI, obtain signature of person providing medical supervision:

Signature _____

g. Describe the process that ensures that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions:

The PI will conduct study meetings with study personnel and assign responsibilities. Bi-weekly research meetings, organized by the budgeted study coordinator, will be held where all personnel are updated on all issues regarding the organization, execution, and follow-up for the study. Scientific meetings will occur weekly (Dr. Walker's weekly lab meeting) to discuss interpretation of research data from the study.

4. Funding

Is this study funded? ☒Yes ☐No

If No, specify that costs of the study will be covered by funds from the UAB department or other source named:_____

If Yes, attach one copy of completed application or request for funding sent to sponsor, and complete a-d.

a. Title of Grant or Contract:

Noninvasive biomarkers to advance emerging DBS electrode technologies in Parkinson's Disease

b. PI of Grant or Contract:

Harrison Walker, MD

c. Office of Sponsored Programs Proposal Number: **000513210**
(*or enter "Pending" and provide upon receipt from OSP*)

d. Sponsor, Funding Route (*check and describe all that apply*):

☒ Gov't Agency or Agencies—Agency name(s):

National Institutes of Health BRAIN Initiative grant number: 1 UH3 NS100553-01. Brain Research through Advancing Innovative Neurotechnologies (BRAIN) http://www.braininitiative.nih.gov/

☐ Department of Defense (DoD): Identify DoD component:_____
☐ Department of Energy (DOE)
☐ Department of Justice (DOJ)
☐ Department of Education
☐ NIH Coop. Group Trial—Group name:_____
☐ Private Nonprofit (e.g., Foundation)—Name:_____
☐ Industry, investigator-initiated—Name:_____ Describe the funding arrangement:_____

Note. Western IRB reviews industry-sponsored protocols unless the investigator initiated the research, or the study qualifies for expedited review or involves gene therapy.

☐ UAB Departmental/Division Funds—Specify:_____

5. Locations Involved

a. Describe the facilities available for the conduct of the research. For research on UAB campus, include building names and room numbers:

University Hospital, UAB Center for Exercise Medicine (UCEM) Neuromechanics and Energetics of Human Performance Laboratory School of Health Related Professions Building; UAB Highlands, TKC, Sparks Center 3rd , 4th and 6th floors,.

b. Indicate all "performance sites" that will provide space, services, facilities, potential or actual participants, or other support for this protocol.

☒ The Kirklin Clinic (TKC)
☒ University of Alabama Hospital (UAHosp)
☐ The Children's Hospital of Alabama (TCHA)
☐ Callahan Eye Foundation Hospital (CEFH)
☒ UAB Highlands
☐ Jefferson County Dept. of Health (JCDH)
☐ Birmingham Veterans Affairs Medical Center (BVAMC)
☐ General Clinical Research Center (GCRC)—inpatient
☐ General Clinical Research Center (GCRC)—outpatient
☐ General Clinical Research Center (GCRC) at The Kirklin Clinic (TKC)
☒ Other (i.e., Any performance site not listed above, including those covered by subcontracts related to this protocol)—Describe:

UAB Center for Exercise Medicine (UCEM) Neuromechanics and Energetics of Human Performance Laboratory in the School of Health Related Professions Building; Sparks Center 3rd, 4th, and 6th floors.

c. Is this study a clinical trial requiring clinical services at one of the performance sites listed in Item b above? ☒Yes ☐No
If Yes, Fiscal Approval Process (FAP)-designated units complete a FAP submission and send to fap@uab.edu. For more on the UAB FAP, see www.uab.edu/osp/clinical-billing-review.

d. Is this a field study? ☐Yes ☒No
If Yes, describe the community and include information about how the community will be involved in the design, implementation and analysis of the research. This would include focus groups, training local facilitators/community health advisors:_____

e. Is the study to be undertaken within a school, business, or other institution that does not have an institutional review board? ☐Yes ☒No
If Yes, attach a statement of any contacts with and approvals from the appropriate institution officials.

Note. Documentation of all such approvals must be received by the UAB OIRB before IRB approval will be issued.

f. Has this protocol or project been reviewed by another IRB, similar review board, or departmental review committee(s) that authorizes the use of its patient populations? ☒Yes ☐No
If Yes, provide name of the review board(s):
Neurology Department Review Committee and for each board listed, enter either the date of latest approval(s) or "PENDING": **10/14/16** or reasons not approved:_____.
If this protocol is subsequently rejected or disapproved by another review board, the UAB IRB must be notified promptly. Attach copies of approvals/disapprovals.

g. Will any of the participants be from the Birmingham Veterans Affairs Medical Center? ☐Yes ☒No
If Yes, attach VA IRB approval or notification from the VA Research and Development Department that the study has been submitted to the VA IRB for review.

h. Will the study be conducted at or recruit participants from the Jefferson County Department of Public Health (JCDH)? ☐Yes ☒No
If Yes, attach notification that the protocol has been approved by JCDH or the Alabama Department of Public Health IRB.

6. Multi-Site Studies

a. Is the investigator the lead investigator of a multi-site study? ☐Yes ☒No
b. Is UAB a coordinating site in a multi-site study? ☐Yes ☒No
c. If you answered **Yes** to *a* or *b*, describe the management of information obtained in multi-site research that might be relevant to the protection of participants. Include, at a minimum, the following items:

- IRB approvals from other sites
- Unanticipated problems involving risks to participants or others. (For example, if there is an unanticipated problem involving risks to participants or others, which site is responsible for reporting it?)
- Interim results.
- Protocol modifications.

_____

7. Drugs: Will any drugs or supplements be used/studied in this protocol? ☐Yes ☒No
If Yes, attach the Drug Review Sheet.

8. Devices: Will any devices be studied in this protocol or used for a purpose other than for which they were approved by the FDA? ☒Yes ☐No
If Yes, attach the Device Review Sheet.

We have attached device review sheets for the Boston Scientific Vercise DBS system with directional leads. We have also attached review sheets for 3 devices that have been previously classified as non-significant risk devices by UAB IRB in different protocols. These include the EEG/ECOG recording system (F140225003 and F140327003) ECOG recording electrodes (F140327003), and our Multichannel Electrical Stimulator (F140225003 and F140327003)

9. Special Approvals

a. Does this project involve the use of radioisotopes? ☐Yes ☒No
If Yes, attach documentation of approval from the Radiation Safety Division.

b. Does this project include patients with contagious infections (e.g., mumps, measles, chickenpox, TB, meningitis)? ☐Yes ☒No
If Yes, attach documentation of approval from Chairman of the Infection Control Committee of the appropriate facilities.

c. Does this project involve obtaining remnant biopsy or surgical material from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Anatomic Pathology Release of Pathologic Materials).

d. Does this project require obtaining any remnant clinical laboratory specimens, body fluids, or microbiological isolates from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Laboratory Medicine Release of Pathologic Materials).

e. Does this project use stored (existing) specimens from a repository? ☐Yes ☒No
If Yes, attach documentation of approval for use of specimens, and describe how existing specimens are labeled:_____

10. Use of Specimens

Does this project involve collecting specimens from participants and storing them for future research? ☐Yes ☒No
If Yes, complete a-h. If no, skip to Item 11

a. How will specimens be obtained, processed, distributed, and stored?

_____

b. How will specimens be labeled (e.g., unique identifier, medical record number, Social Security number, name, date of birth)?

_____

c. How will clinical data associated with the specimens be collected and stored?

_____

d. What participant-identifying information will be collected and linked to the specimens?

_____

e. What steps will be taken to maximize the confidentiality of linked identifiers? For example, procedures could include using a password-protected computer database to link identifiers, with limited personnel knowledgeable of the password, or coded identifiers released without the ability to link to clinical data (also called "stripped" or "anonymized" specimens).

_____

f. Will specimens be shared with other investigators in the future? ☐Yes ☐No
If Yes, what identifiers, clinical information and demographic information will be shared; or will the specimens be stripped of identifiers (i.e., anonymized)?

Also **if yes**, outline your procedure for assuring IRB approval for release and use prior to release of specimens.

Note. Investigators who receive and/or use these specimens must document approval from the appropriate IRB(s) before the specimens may be released.

g. Will biological samples be stored for future use? ☐Yes ☐No
If Yes, indicate whether they will be used for the disease under study in this protocol or research on other diseases.

h. Is genetic testing planned? ☐Yes ☐No
If Yes, describe the planned testing here and see "DNA/Genetic Testing" in the Guidebook for consent requirements.

11. Gene Therapy

Does this project involve gene therapy or administering recombinant materials to humans? ☐Yes ☒No
If Yes, submit the Gene Therapy Project Review Panel Report –OR- If this is a vaccine trial that is exempt from the NIH Guidelines For Research Involving Recombinant DNA Molecules, submit the Protocol Oversight Review Form For Clinical Vaccine Trials.

12. HIPAA Privacy and Security

Will the PI or others obtain, review, or make other use of participants' "personal health information" (i.e., information, whether oral or recorded in any form or medium that (a) is created or received by a health care provider and (b) relates to past, present, or future physical or mental health or condition of an individual; or provision of health care; or payment for provision of heath care)? ☒Yes ☐No

If Yes, complete a-e as described.

a. Will the data/information be stored or managed electronically (on a computer)? ☒Yes ☐No

b. Is the principal investigator requesting that the UAB IRB waive patient HIPAA authorization from another institution or entity (e.g., insurance company, collaborating institution). ☐Yes ☒No
If Yes, attach copy of privacy notices from institution/entity, and provide the name of institution/entity:_____

c. Indicate which, if any, of the listed entities below would provide information or maintain health information collected for this protocol and/or where health information that been collected will be stored/maintained.
- ☒ The Kirklin Clinic
- ☒ University of Alabama Hospital
- ☐ The Children's Hospital of Alabama
- ☐ Callahan Eye Foundation Hospital
- ☒ UAB Highlands
- ☐ Jefferson County Department of Health
- ☐ School of Dentistry

☐ School of Health Professions
☐ School of Medicine
☐ School of Nursing
☐ School of Optometry
☐ University of Alabama Health Services Foundation
☐ UAB Health Centers
☐ Viva Health
☐ Ophthalmology Services Foundation
☐ Valley Foundation
☐ Medical West - UAB Health System Affiliate
Health System Information Systems:
☐ HealthQuest
☒ Cerner Millennium (Lab, Radiology, UED, Surgery)
☒ EMMI - Master Member Index
☒ Horizon - IPV (IVR/CDA/CRIS)
☐ CareFlow Net
☐ Eclipsys (PIN)
☒ IMPACT
☐ None—**If None, skip to Item 13.**

d. Indicate which of the listed identifiers would be associated/linked with the protected health information (PHI) used for this protocol.
☒ Names
☒ Geographic subdivisions smaller than a State
☒ Elements of dates (except year) related to an individual
☒ Telephone numbers
☐ Fax numbers
☐ Email addresses
☐ Social security numbers
☒ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers
☒ Device identifiers and serial numbers
☐ Biometric identifiers
☐ Web universal resource locators (URLs)
☐ Internet protocol address numbers
☒ Full-face photographic images (camera images as described in 16a)
☒ Any other unique identifying number—Describe: **subject id**
Note. Codes are not identifying as long as the researcher cannot link the data to an individual
☐ None—**If None, skip to Item 13.**

e. Choose one plan to describe your use of the personal health information:
☐ The data collected meet the specifications for a "limited data set"
—Attach Data Use Agreement or Business Associate Agreement
☒ Research staff will obtain authorization from each patient to use the information

—Attach Patient Authorization form, complete except for patient name and IRB protocol number

☐ PI requests Waiver of Patient Authorization to use the information
—Attach Waiver of Authorization and Informed Consent form

PROPOSED RESEARCH

- The IRB will not accept grant applications and/or sponsor's protocols in lieu of the items as outlined below.
- Do not separate responses from items. Instead, insert your response to each item below the item, keeping the information in the order of this form.
- Number each page of the Human Subjects Protocol (i.e., Page *X* of *Y*).

13. Purpose—in nontechnical, lay language

Summarize the purpose and objectives of this protocol, including any related projects, in one short paragraph.

Although deep brain stimulation (DBS) can be remarkable for treating symptoms of Parkinson's disease, improvement varies across clinical trials, individual patients, and over time. A major limitation to the advancement of DBS therapy is that there are no established biomarkers to tailor stimulator settings in individuals. Emerging segmented ("directional") lead technology will allow current steering, a new opportunity to shape the electrical field associated with DBS in individual patients to improve tolerability and efficacy. This novel lead design (see schematic for the DBS lead and surrounding electrical field in red in the inset) has 8 contacts rather than the 4 available with currently available leads. How do we optimally adjust stimulation parameters in a patient when there are far more potentially useful settings than can be practically evaluated in clinic? How do we know that DBS settings in a given patient are optimal or appropriate? We have pioneered minimally invasive, rapidly acquired biomarkers to solve these important problems. Using EEG and ECOG to analyze cortical activity, the electrophysiological data we acquire from our electrode array serves as the putative and investigated biomarker. Thus, the purpose of this research is to explore whether this stimulus-evoked cortical physiology predicts the optimal combination of active contacts with newly available directional DBS electrode technology provided by our industry partner Boston Scientific.

14. Background—in nontechnical, lay language

Summarize in 2-3 paragraphs past experimental and/or clinical findings leading to the formulation of this study. Include any relevant past or current research by the Principal Investigator. For drug and device studies summarize the previous results (i.e., Phase I/II or III studies).

Next-generation "directional" lead designs provide an unprecedented opportunity to address deficiencies of conventional DBS. Despite its critical importance to outcomes and relevance to all DBS patients, device adjustments after surgery are relatively neglected as a research topic. With an almost unlimited number of potential stimulation parameters, routine DBS programming is a time-consuming, labor-intensive trial and error process. This therapeutic challenge is growing exponentially with the introduction of new technologies that offer various forms of current steering and fractionation. These new approaches promise to selectively activate specific motor circuits in individuals, not only to avoid common dose limiting side effects, but also to improve resistant motor symptoms such as freezing of gait and overall efficacy. Early studies from Europe show feasibility and safety but are only beginning to realize the potential of this emerging technology.

Here we propose a novel, first-in-human approach using both behavior and cortical activation patterns to guide field shaping ("current steering") with emerging directional DBS lead technology. Our results will provide methods to tailor activation and adjustment of combinations of DBS electrode contacts in individuals to more fully engage the spatial extent of the therapeutic target, based on the surrounding functional anatomy. Our current steering approach addresses critical needs (1) to improved patient-perceived DBS outcomes, (2) to optimize surgical and clinical efficacy, (3) to lessen potential dose-limiting side effects, (4) to better treat resistant motor symptoms such as freezing and other gait disturbances, (5) to broadly improve the consistency of the clinical response, (6) to streamline and expedite device activation and adjustment after surgery, (7) to improve battery efficiency, and (8) to accomplish each of these goals with real-time guidance from objective, patient-specific biomarkers.

Commercially available DBS leads in the US consist of a linear array of ring-shaped electrodes. We are studying segmented leads developed by Boston Scientific to steer current and better optimize DBS efficacy and tolerability in individuals. Evidence from recent studies in Europe by Timmermann et al and Volkmann et al suggest that this current steering approach is feasible for these purposes, however it is possible that the activation of individual segments alone will not provide therapeutic benefit or that they will not improve the thresholds for potential side effects from DBS in individual patients. If this were the case, we can still activate all three segments simultaneously so that the individual segments act together as a traditional ring electrode.

15. Participants (Screening and Selection)

a. How many participants are to be enrolled at UAB? **40**
If multi-center study, total number at all centers:
Not applicable, this is a single center study

b. Describe the characteristics of anticipated or planned participants.
Sex: **Both**
Race/Ethnicity: **All**
Age: **18 - 70**
Health status:

Patients who undergo deep brain stimulation (DBS) as part of routine care for Parkinson's Disease

Note. If data from prior studies indicate differences between the genders or among racial/ethnic groups in the proposed research or if there are no data to support or to negate such differences, Phase 3 clinical trials will be required to include sufficient and appropriate entry of gender and racial/ethnic subgroups so that trends detected in the affected subgroups can be analyzed. If ethnic, racial, and gender estimates are not included in the protocol, a clear rationale must be provided for exclusion of this information. If prior evidence indicates that the results will not show gender or racial differences, researchers are not required to use gender or race/ethnicity as selection criteria for study participants. They are, however, encouraged to include these groups. See Section II. Policy of the NIH POLICY AND GUIDELINES ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH – Amended, October, 2001) for further details.

c. From what population(s) will the participants be derived?

Participants will be identified from the clinics of Dr. Walker and other neurologists who specialize in movement disorders at UAB. Participants will be recruited from the population of patients who have elected to undergo DBS surgery at our Movement Disorders Center as part of routine care. We place greater than 100 DBS electrodes per year for patients with movement disorders, and we propose enrolling 40 patients with Parkinson's disease over the 5 year funding period.

Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants:

Dr. Walker and other study personnel have ample access to this patient population in their TKC clinics.

Describe the inclusion/exclusion criteria:

Inclusion criteria:

1. **Age ≥18 years and ≤70 years.**
2. **Clinically definite, advanced idiopathic PD based on at least 2 of 3 cardinal PD features (tremor, rigidity, or bradykinesia).**
3. **Disease duration of 4 years or more.**
4. **Participant has elected to undergo DBS surgery as part of routine care, and the subthalamic nucleus (STN) is recommended as the surgical target.**
5. **Participant agrees to not undergo contralateral DBS for the other side of the brain until ≥ 12 months after initial DBS surgery.**
6. **Participant is healthy enough to undergo surgery and the research protocol.**
7. **Normal, or essentially normal, preoperative brain MRI.**
8. **Willingness and ability to cooperate during awake DBS surgery, as well as during post-operative evaluations, adjustments of medications and stimulator settings.**
9. **Participant's health insurance and/or Medicare covers DBS surgery as part of routine care.**
10. **Refractory motor symptoms such as tremor, dyskinesias, wearing off, and/or motor fluctuations, causing significant disability or occupational dysfunction, despite reasonable attempts at medical management, as determined by our consensus DBS committee.**
11. **Stable doses of PD medications for at least 28 days prior to baseline assessments.**
12. **Improvement of motor signs ≥30% with dopaminergic medication as assessed with the use of the Movement Disorders – Unified Parkinson's Disease Rating Scale, part III (MDS-UPDRS III; scores range from 0 to 108, with higher scores indicating worse functioning).**
13. **Disease severity ratings above Hoehn and Yahr stage 1, defined as unilateral involvement only with minimal or no functional disability, with scores ranging from 0 to 5 and higher scores indicating more severe disease.**
14. **Score of more than 6 for activities of daily living in the worst "off" medication condition despite medical treatment, as assessed with the use of the MDS-UPDRS II (scores range from 0 to 52, with higher scores indicating worse functioning), or mild-to-moderate impairment in social and occupational functioning (score of 51 to 80% on the Social and Occupational Functioning Assessment Scale with scores ranging from 1 to 100 and lower scores indicating worse functioning).**
15. **Dementia Rating Scale-2 (DRS-2) score of ≥130 on medications.**
16. **Beck Depression Inventory II (BDI-II) score of ≤25 on medications.**
17. **Participant expresses understanding of the consent process, terms of the study protocol, is available for follow-up over the length of the study, and signs informed consent.**

Exclusion criteria:

1. **Age <18 years or >70 years.**
2. **Participant's insurance will not cover the costs of surgery with the investigational device.**
3. **Medical contraindications such as current uncontrolled hypertension, heart disease, coagulopathy, or other conditions contraindicating DBS surgery or stimulation.**
4. **Duration of disease of <4 years**
5. **Participant or care team determine that contralateral DBS for the other side of the brain will likely be clinically indicated <12 months after initial DBS surgery.**
6. **Diagnosis or suspicion of atypical parkinsonism (progressive supranuclear palsy, multiple system atrophy, corticobasal syndrome) or drug-induced parkinsonism, or significant neurological disease other than Parkinson's disease.**
7. **Disease severity ratings of Hoehn and Yahr stage 1, defined as unilateral involvement only with minimal or no functional disability, with scores ranging from 0 to 5 and higher scores indicating more severe disease.**
8. **Diagnosis of psychogenic movement disorder based on consensus criteria.**
9. **Score of >25 on the Beck Depression Inventory II, with scores ranging from 0 to 63 and higher scores indicating worse functioning), or history of suicide attempt.**
10. **Any current acute psychosis, alcohol abuse or drug abuse.**
11. **Clinical dementia (score of ≤130 on the Mattis Dementia Rating Scale with scores ranging from 0 to 144 and higher scores indicating better functioning).**
12. **Ongoing or pervasive impulse control disorder not resolved by reduction of dopaminergic medications.**
13. **Use of anticoagulant medications that cannot be discontinued during perioperative period.**
14. **History of hemorrhagic stroke.**
15. **Current or future risk of immunocompromise that might significantly increase risk of infection.**
16. **History of recurrent of unprovoked seizures.**
17. **Lack of clear levodopa responsiveness.**
18. **Any medical condition requiring repeated MRI.**
19. **The presence of an implanted device (e.g., cochlear implant, pacemaker, neurostimulators), whether turned on or off.**
20. **Prior DBS surgery or ablation within the affected basal ganglion.**
21. **A condition requiring or likely to require the use of diathermy.**
22. **Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.**
23. **Any medical or psychological problem that would interfere with the conduction of the study protocol**
24. **A female who is breastfeeding or of child-bearing potential with a positive urine pregnancy test or not using adequate contraception.**

d. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group.

Not applicable.

e. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.

☐ Pregnant Women: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates

☐ Fetuses: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates

☐ Neonates/Nonviable Neonates: SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Prisoners: Attach SPRF—Prisoners
☐ Minors (<18 years old): Attach SPRF—Minors
☒ Employees or students at institution where research conducted
☐ Persons who are temporarily decisionally impaired
☐ Persons who are permanently decisionally impaired (e.g., mentally retarded)

☐ Non-English Speakers

For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion:

We occasionally have patients in our clinic who work at UAB, an employer of more than 20,000 people in the Birmingham metro area. Their participation is completely voluntary, and it is very unlikely that they would be directly linked to the PI or study team with respect to their work responsibilities. We would not consent patients who work immediately with or under any study personnel, and we would emphasize the voluntary nature of the study and that enrolling or not enrolling would have no bearing on their status as an employee or as a student otherwise.

f. List any persons other than those directly involved in the study who will be at risk. If none, enter "None": **None.**

g. Describe the process (e.g., recruitment, chart review) that will be used to seek potential participants (e.g., individuals, records, specimens). Research recruitment by non-treating physicians/staff may require completion of Partial Waiver of Authorization for Recruitment/Screening. (See http://main.uab.edu/show.asp?durki=61981.)

Upcoming patient schedules and charts for the Movement Disorders Clinic will be reviewed for participants who might meet eligibility criteria, and either Dr. Walker, Dr. Guthrie, Christopher Gonzalez, Ashlie Cassidy or Julie Boyd will approach and consent patients who are considering undergoing DBS surgery during routine care encounters. Patients will not be consented to participate in the study until they have elected to undergo DBS as part of routine care.

h. If you will use recruitment materials (e.g., advertisements, flyers, letters) to reach potential participants, attach a copy of each item. If not, identify the source (e.g., databases) from which you will recruit participants.

None at this time.

i. Describe the procedures for screening potential participants.

As indicated above, Dr. Walker and his study personnel will review the patient records of the upcoming movement disorders clinic patients to screen for eligibility. Dr. Walker or one of the other study personnel with consent privileges will approach potential subjects meeting the inclusion criteria and having no exclusion criteria during a routine care encounter in clinic.

Subjects will have at least 24 hours to discuss participation with their family and physician and to decide if they would like to participate in the study.

16. Protocol Procedures, Methods, and Duration of the Study—in nontechnical language

a. Describe the procedures for all aspects of your study. Tell us what you are doing.

Research Encounters: We utilize objective clinical instruments that are normed and validated in order to measure changes in motor and non-motor disability related to PD. All participants will complete four comprehensive assessment batteries to better understand and guide the implementation of field shaping with novel directional DBS lead technology. Many of the research visits are incorporated as extensions of routine care encounters that would have occurred regardless of study participation. On a per-participant basis, all study encounters are completed within 9 months of surgery, although we will continue enrolling new participants through year 4 of funding. After completion of the research encounters, all participants will be followed in an open-label fashion per routine care every 6 months (or more frequently, if necessary). In all acute behavioral studies, we allow 5 minutes for adjustment/acclimation to changes in DBS settings done as SOC prior to testing efficacy.

Motor battery. Pre- and post-op motor assessments are part of routine care for patients with Parkinson's disease. The motor assessments for this study are more extensive and frequent than what occurs as part of routine care. These assessments will be conducted over multiple sessions in the Neuromechanics Laboratory (Chris Hurt, PhD, sub-investigator). In the "practically defined off" medication state (off PD medications for >12 hours), we will measure changes in the cardinal PD symptoms (tremor, rigidity, bradykinesia, dyskinesias) observationally using the UPDRS-part 3 (a standard neurological measure for the diagnosis of movement disorders), along with measures of upper limb dexterity (9-hole pegboard dexterity test, this is a timed test requiring the participant to place 9 separate pegs into holes in a standardize block and then remove them), gait (4-meter walk gait speed, walking backwards, both of these are timed tests require patients to walk given distances), postural stability (limits of stability test, the floor beneath the participant is moved until the patient becomes unstable. Safety is ensured through the use of a safety harness.), compensatory stepping (compensatory stepping test, analyzes stepping patterns and the forces generated by the feet of patients), balance (The activities-specific balance confidence (ABC) scale), and posture (static posture test, a simple observation of the participant's posture) versus pre-op baseline. Further, movements will be measured with 8 camera 3-D motion capture and treadmill force plates, allowing complete parameterization of upper limb dexterity, gait, balance, and other complex movement abnormalities associated with PD. Motor assessments will be obtained prior to surgery and with repeated measures after each portion of the crossover study. This core motor battery will last no more than 1 hour total.

Cognitive/behavioral, speech, and quality of life batteries: Pre-op neuropsychological testing is part of routine care, however all post-op NP testing is study-related. The medical record will be reviewed for the pre-op testing data. For patient comfort, these evaluations will occur on a different day from the motor battery in the Neuropsychology Laboratory (Roy Martin, PhD, sub-investigator), with patients on their dopaminergic medications. This battery will measure changes in sensitive, validated measures of verbal fluency, executive function, planning, memory, impulsivity, anxiety, depression, speech intelligibility and acoustics, and patient-centered quality of life assessments versus pre-op baseline. The specific cognitive measures used are the Dementia rating scale-2 (DRS-2), Oral reading recognition, Conners Continuous

Performance Test (CPT-3), Flanker inhibitory control, List sorting working memory, Animals, fruits, and vegetables, Picture vocabulary, AVLT, 10/36 spatial memory, Picture sequence memory, Judgement of line orientation, Trails A and B, Pattern comparison processing, Letter fluency (alt forms), DKEFS Stroop test, Picture vocabulary, Dimensional change card sort, Neuropsychiatric inventory, Beck depression inventory-2 (BDI-2), and the Beck anxiety inventory. Quality of life measures include PD questionnaire 39 (PDQ-39), Freezing questionnaire (FOG-Q), UPDRS-parts 1, 2, and 4, a motor function diary kept by the participant, and an open ended interview. The speech measures include the Rainbow passage, Voice handicap index, Communicative index bank, as well as assessments of spontaneous speech, maximum phonation time, and voicing formants F1 and F2. This comprehensive assessment will last no more than 3 hours per session.

Intraoperative ERP assay: DBS surgery occurring electively as part of routine care. We only consent patients after the patient has been approved for surgery for routine care. Our research approach in the OR uses a unique electrophysiological assay to measure cortical activation by DBS with high bandwidth simultaneous EEG, ECOG (over pre-motor, primary motor, and primary sensory cortices), and 8 contralateral surface EMG electrodes. We measure cortical activation by DBS in a dose-dependent manner, elicited from the entire spatial extent of the implanted lead. EEG, ECOG, and EMG are validated modalities that have been in worldwide clinical use for decades. As such, putative biomarkers from this study have the potential for broad, immediate application. Our unique electrophysiology approach allows (1) remarkable stimulus artifact removal; (2) accurate detection of small differences in ERP latency; (3) explicit control of the timing, waveform, and pattern of the stimuli, (4) fully automated stimulus protocol delivery, and (5) markedly faster post-processing. This allows us to evaluate hypotheses that were untestable in prior DBS studies. We use our externalized pulse generator to randomize stimulus amplitude (0 to 5 mA in 1 mA increments), location (anode/cathode pair), and interstimulus interval (mean 100±20 ms) on a pulse by pulse basis. We will elicit ERPs only from adjacent electrode pairs, yielding 25 stimulation conditions. Based on extensive prior work, 100 stimulation events (50 in each anode/cathode pair) is more than sufficient to generate an ERP in the vast majority of participants. The total duration of the assay is 24.0 minutes.

Neuroimaging Battery: All imaging studies including MRI and CT occur as part of routine care. Data from the imaging studies will be used for research purposes. Imaging will occur (1) pre-operatively for screening and diagnostic purposes, (2) to inform routine stereotaxy on the day of surgery, (3) to localize ECOG, EEG, and DBS electrodes during surgery, and (4) to confirm lead placement and screen for potential adverse events after surgery.

Monopolar Survey: The DBS device is activated approximately one month after surgery as part of routine care in a session called the monopolar survey. Because of the special design of the directional lead used in this study, the monopolar survey will take longer than that for routine care. In this encounter we will optimize the participant's DBS as if it were a conventional DBS system. We will also assess the therapeutic window of each electrode contact. Therapeutic window is a useful continuous measure of the available range of DBS intensities at a given stimulation site that provides motor improvement without intolerable side effects. For our purposes, the floor of the therapeutic window is defined as the lowest stimulus amplitude that markedly improves arm rigidity, whereas the ceiling amplitude elicits either involuntary contraction of the contralateral mouth or arm because of corticospinal activation or noticeably worsens PD symptoms.

Crossover Study: In a balanced design, we will randomly allocate patients to three different conditions, each over two month intervals, (1) conventional DBS guided by behavioral testing

(UPDRS, pegboard dexterity, gait speed test, and dynamic balance/posture measures (see motor battery above for descriptions)), (2) multiple active contacts selected based on behavioral testing, and (3) multiple contacts selected by cortical physiology alone. In the first month of each randomization period, participants will be allowed to adjust stimulus amplitude at home, within safety limits defined by therapeutic window measures from the monopolar survey. Patient adjustment of DBS settings at home has been part of routine care for years. They will remain on this preferred amplitude for the second month of the randomization period and then return at the end for motor and non-motor assessments. Motor outcomes for the crossover will include repeat UPDRS part 3, pegboard dexterity, gait speed test, and posture/balance measures from the Motor Battery (discussed previously).

During the Motor Battery assessments in the crossover, we will conduct Field Shaping Surveys to determine whether tailored activation of combinations of DBS contacts, guided by patient-specific network physiology, predicts changes in therapeutic window (the range of therapeutically effective stimulus amplitudes versus omnidirectional DBS). They will occur in the motor assessments at the conclusion of the first two crossover conditions. While in the operating room we will measure stimulus evoked activity and local field potential data through the DBS lead in response to hand, leg, and mouth movements. In addition to the primary study outcomes comparing directional versus omnidirectional DBS, we will use these encounters to determine if specific combinations of DBS contacts, guided by stimulus evoked activity and local field potentials in surgery, improve motor symptoms. Behavioral measures will include therapeutic window, MDS-UPDRS Part III, pegboard dexterity, gait speed test, and dynamic balance/posture measures (see motor battery above for descriptions) across different combinations of contacts on the segmented lead.

Non-motor assessments will occur on a different day and include patient-reported quality of life measures, cognitive/behavioral, and speech batteries (discussed previously). At study conclusion, we will conduct an open-ended exit interview to ask patients about their overall experience, to rank the programming strategies from the crossover study from best to worst, and explain their rationale for the rankings.

Exploratory Crossover Arm Guided by Electrophysiology Biomarkers. These encounters and treatment assignments occur as part of research. Based on safety and tolerability testing from the field shaping survey, we will activate a combination of one or more DBS contact segments based purely on electrophysiology from the intraoperative assay over the next two months. Similar to the randomized crossover, participants will be allowed to adjust stimulus amplitude at home during the first month, within safety constraints defined by therapeutic window measures from the field shaping survey. They will remain on their preferred amplitude for the second month of the randomization period and then return at the end for motor and non-motor assessments. Motor outcomes for the crossover will include repeat UPDRS part 3, pegboard dexterity, gait speed test, and posture/balance measures from the Motor Battery (discussed previously). Non-motor assessments will occur on a different day and include patient-reported quality of life measures, cognitive/behavioral, and speech batteries (discussed previously). At study conclusion, we will again collect data regarding patient preference, ranking the various programming strategies from the crossover study from best to worst, and explain their rationale for their treatment preference.

Study Exit = visit with repeated outpatient EEG assay: This encounter will serve as a 1 year post-operative follow up visit that would normally be a part of routine care. We will repeat the Motor Battery at this time as well. To test the long-term robustness of our electrophysiological measures we will retest the electrophysiological assay conducted 1 year prior in the operating room, measuring cortical activation by DBS with EEG and 8 contralateral surface EMG

electrodes. We will not measure ECoG during this assay because this modality is only available during surgery (we remove the ECoG strip after testing in the OR). In this post-op visit, the implanted Boston Scientific pulse generator will provide the electrical stimulation. We will elicit cortical responses from stimulation from adjacent electrode contact pairs in a similar manner to our protocol during surgery. The total duration of the assay is approximately 30 minutes.

b. What is the probable length of time required for the entire study (i.e., recruitment through data analysis to study closure)?

5 years

c. What is the total amount of time each participant will be involved?

1 year

d. If different phases are involved, what is the duration of each phase in which the participants will be involved? If no phases are involved, enter "not applicable."

Pre-op baseline evaluation: Involves two study visits. One is a motor battery (see 16a above) visit lasting approximately one hour and the other is one cognitive/speech/quality of life evaluation (see 16a above) lasting approximately 3 hours. The pre-op baseline evaluation will take place during month one following enrollment.

DBS implantation surgery: Typical DBS surgeries last between 2-3 hours. Here we will measure cortical activation by DBS with EEG/ECOG/EMG. The actual research portion on the day of surgery will extend the surgical time by no more than 30 minutes. As per routine care, O-arm CT images and post-op MRI images that we will use for DBS lead localization will be gathered as well. DBS electrode implantation surgery will take place during month 2 following enrollment.

Monopolar survey: Here the participant's DBS will be activated and therapeutic settings will be identified. This involves a clinical visit and lasts approximately two hours. In addition, we will assess the participant's movement abilities with our motor battery (see 16a above) lasting approximately one hour. The monopolar survey will take place during month 3 following enrollment.

Crossover study: This portion of the study will involve six separate study visits over the course of 6 months to evaluate three different DBS stimulation conditions. For each condition we will assess our motor battery and field shaping surveys in one visit (see 16a above) lasting approximately one hour and our cognitive/speech/quality of life batteries (see 16a above) in one visit lasting approximately 3 hours. Also, see Table 3 below.

TABLE 3. Summary of research encounters, procedures, and corresponding specific aims.	Pre-op baseline		DBS surgery	Monopolar Survey	Double-blind, randomized crossover to omnidirectional versus directional DBS guided by monopolar survey				Crossover to directional DBS guided by EEG/ECoG		Study exit at 1 year with repeat EEG
					Condition 1		Condition 2		Condition 3		
Specific Aim(s)	All			1.1 and 1.2	2.1, 2.2, and 2.3						
Encounter number	1a	1b	2	3	4a	4b	5a	5b	6a	6b	7
Encounter duration (hours)	1	3	3-4	3	3	3	3	3	3	3	3
Calendar duration (months)	1		2	3 to 4			5 to 6				12
Medication state	off	on	off	off	on	off	on	off	on	off	off
Motor battery											
Cognitive/behavioral battery											
Quality of life battery											
Speech battery											
Field shaping survey											
PRISMA MRI with tractography											
ERP assay (EEG/ECOG/EMG)											
O-arm CT for lead localization											
Routine post-op CT brain											

Exploratory Crossover Arm Guided by Electrophysiology Biomarkers: In this nested arm of the crossover study, we will activate a combination of one or more DBS contact segments based purely on electrophysiology from the intraoperative assay. It will involve two study visits over the course of 2 months. For this condition we will assess our motor battery in one visit (see 16a above) lasting approximately one hour and our cognitive/speech/quality of life batteries (see 16a above) in one visit lasting approximately 3 hours.

Study Exit visit: This portion of the study will involve a single visit to serve as a 1 year post-operative follow up to evaluate the long term robustness of our electrophysiological measures. We will reassess portions of our motor battery (see 16a above) and our ERP assay. This visit should last less than 2 hours.

e. List the procedures, the length of time each will take, and the frequency of repetition, and indicate whether each is done solely for research or would already be performed for treatment or diagnostic purposes (routine care) for the population. *Insert additional table rows as needed.*

Please see table 3 above for frequency of repetition. Each measure will be assessed once at each indicated visit.

Procedure	***Length of Time Required of Participants (minutes)***	***Frequency of Repetition***	***Research (Res) – OR- Routine Care***
Measures acquired during DBS surgery			
Intra-op ERP assay	≤30	1 repetition	☒Res ☐Routine
Intra-op O-arm CT	10		☐Res ☒Routine
Post-op brain MRI	30		☐Res ☒Routine
total time (beyond routine care)	≤30		
Motor battery			
UPDRS-part 3	5	7 repetitions (pre-op; monopolar	☐Res ☒Routine
Therapeutic window	30		☐Res ☒Routine

Activities-specific balance confidence (ABC) scale	3	survey; cross-over visits 4a, 5a, and 6a)	☒Res ☐Routine
9-hole pegboard dexterity	1		☒Res ☐Routine
4-meter walk gait speed	3		☒Res ☐Routine
Walking backwards	3		☒Res ☐Routine
Compensatory stepping	3		☒Res ☐Routine
Static posture	2		☒Res ☐Routine
Limits of stability	2		☒Res ☐Routine
total time (beyond routine care)	17 per encounter		
Cognitive/behavioral battery			
Dementia rating scale-2	20	4 repetitions (pre-op; cross-over visits 4b, 5b, and 6b)	☒Res ☐Routine
Oral reading recognition	3		☒Res ☐Routine
CPT-3	14		☒Res ☐Routine
Flanker inhibitory control	3		☒Res ☐Routine
List sorting working memory	7		☒Res ☐Routine
Animals/fruit/ vegetables	5		☒Res ☐Routine
Picture vocabulary	4		☒Res ☐Routine
AVLT (with alt forms)	15		☒Res ☐Routine
10/36 Spatial memory	15		☒Res ☐Routine
Picture sequence memory	7		☒Res ☐Routine
Judgement of line orientation	5		☒Res ☐Routine
Trails A and B	10		☒Res ☐Routine
Pattern comparison processing	3		☒Res ☐Routine
Letter fluency (alt forms)	3		☒Res ☐Routine
DKEFS Stroop test	10		☒Res ☐Routine
Picture vocabulary	7		☒Res ☐Routine
Dimensional change card sort	4		☒Res ☐Routine
Neuropsychiatric inventory	15		☒Res ☐Routine
Beck depression inventory-2	7		☒Res ☐Routine

Beck anxiety inventory	7		☒Res ☐Routine
total time (beyond routine care)	164 per encounter		
Quality of life battery			
PD questionnaire 39 (PDQ-39)	15	4 repetitions (pre-op; cross-over visits 4b, 5b, and 6b)	☒Res ☐Routine
Freezing questionnaire (FOG-Q)	7		☒Res ☐Routine
UPDRS-parts 1, 2, and 4	30		☒Res ☐Routine
Motor function diary	15		☒Res ☐Routine
Open ended interview	30		☒Res ☐Routine
total time (beyond routine care)	67 per encounter		
Speech battery			
Rainbow passage	3	4 repetitions (pre-op; cross-over visits 4b, 5b, and 6b)	☒Res ☐Rout
Spontaneous speech	5		☒Res ☐Rout
Maximum phonation time	3		☒Res ☐Rout
Sustained phonation of vowels	3		☒Res ☐Rout
Formants (F1 and F2)	5		☒Res ☐Rout
Voice handicap index	10		☒Res ☐Rout
Communicative index bank	2		☒Res ☐Rout
total time (beyond routine care)	31 per encounter		
Study Exit visit			
ERP assay	≤30	1 repetition	☒Res ☐Routine
UPDRS-part 3	5		☐Res ☒Routine
Therapeutic window	30		☐Res ☒Routine
9-hole pegboard dexterity	1		☒Res ☐Routine
4-meter walk gait speed	3		☒Res ☐Routine
total time (beyond routine care)	≤34		

f. Will an interview script or questionnaire be used? ☒Yes ☐No
If Yes, attach a copy.

g. Will participants incur any costs as a result of their participation? ☒Yes ☐No
If Yes, describe the reason for and amount of each foreseeable cost.

Patient (if pursuing surgery as self-pay) or their insurance will be charged for the surgery and clinical f/u visits.

h. Will participants be compensated? ☒Yes ☐No

If Yes, complete i-v:

i. Type: (e.g., cash, check, gift card, merchandise):
Check or direct deposit (only UAB personnel and students). We are also planning on making a 3D printed brain for participants at the completion of the study based on their pre-op brain MRI.

ii. Amount or Value:
$70 per study visit. On a case by case basis, for participants who live >50 miles from the Birmingham metropolitan area we will provide ≤$200 for hotel room, mileage, and meals.

iii. Method (e.g., mail, at visit):
Mail or direct deposit (only UAB personnel and students). We will give them their 3D printed brain at the last study visit.

iv. Timing of Payments: (e.g., every visit, each month):
Within 30 days of each visit

v. Maximum Amount of Payments per Participant:
$490 ($70 after each of 7 possible study visits).

17. Describe the potential benefits of the research.

This study has the potential to benefit patients in a number of ways. We may develop a better way to activate the device that provides more efficacy, fewer side effects, more efficient battery usage, less cognitive or behavioral side effects, improvements in walking/balance, and/or improvements in speech. Additionally our use of cortical physiology biomarkers might allow us to reach these settings faster and more efficiently, rather than through the tedious trial-and-error process of routine DBS adjustments. Even if this does not benefit patients directly, the knowledge gained may eventually help us to better optimize surgical targeting and clinical adjustment of the DBS device to improve efficacy and tolerability. A benefit for some of the participants is that we obtain very detailed information about how DBS alters their symptoms, more than is typically derived from routine care alone. Although this can provide tangible benefits in some patients, it is not an explicit goal of the study.

18. Risks

a. List the known risks—physical, psychological, social, economic, and/or legal—that participants may encounter as a result of procedures required in this protocol. Do not list risks resulting from standard-of-care procedures. *Note. Risks included in this protocol document should be included in the written consent document.*

1. **Participation in any human research poses a risk of the loss of privacy. All human subjects protocol risk the loss of privacy.**

2. **Additional surgical time: Additional time beyond routine care will be required to conduct our experiments in the operating room. The sterile field will not be compromised and the brain will be physically manipulated only slightly beyond what is routine by virtue of placing a small, smooth cortical electrode array on the brain at the time of DBS implant (see risk 6 below), the length of the DBS procedures will increase by 0-30 minutes. This increased surgery time could potentially introduce a small increase in the risk for postoperative infection beyond the**

~2% infection rate at 5 years follow up that we have recently demonstrated in a series of more than 500 consecutive patients. The potential incremental risk related to increased surgical time is likely very small, but we would be positioned to detect such a risk based on our prior research on this topic.

3. Boston Scientific Vercise PC and Directional Lead. With commercial DBS devices, there can be various forms of mechanical and/or electrical failure, including battery leakage, battery failure, lead or extension breakage, hardware malfunctions, loose connections, electrical shorts or open circuits, and lead insulation breaches. These potential failures may require various levels of surgical revision, including potentially revision of the entire system including craniotomy. Whether these kinds of issues are more or less common with the Boston Scientific device is unclear.

4. Directional brain stimulation: Commercially available DBS leads in the US consist of a linear array of ring-shaped electrodes. We are studying segmented leads developed by Boston Scientific to steer current and better optimize DBS efficacy and tolerability in individuals. Evidence from recent studies in Europe by Timmermann et al and Volkmann et al suggest that this current steering approach is feasible for these purposes, however it is possible that the activation of individual segments alone will not provide therapeutic benefit or that they will not improve the thresholds for potential side effects from DBS in individual patients.

5. MRI compatibility of Boston Scientific Vercise PC Implanted Pulse Generator: Similar to other commercially available devices, the Boston Scientific Vercise PC battery has not been, nor will it ever be, declared safe for brain or body MRI. If participants require contralateral DBS for the other side of their brain, lack of MRI on the day of their second surgery could potentially compromise targeting of the implanted electrode in some cases.

6. "Off" medication assessments: To minimize travel and expense for participants, research studies are arranged on days when participants would be scheduled for follow-up appointments whenever possible, and many of the relevant clinical outcomes are obtained as part of routine care visits. DBS patients routinely arrive for clinic evaluations "off" their dopaminergic medications, both as part of DBS surgery and stimulation adjustments for routine care. Additionally, these "off" meds assessments are a standard practice for participation in surgical trials for PD.

7. Electroencephalography (EEG): The BrainVision ActiChamps 64 channel EEG system has been classified as a non-significant risk device by the UAB IRB in other protocols. EEG recordings are performed during surgery and at a Study Exit visit. EEG is non-invasive, readily administered, and portable. An array of electrodes is attached to the scalp on the day of the study.

8. Electrocorticography (ECOG): The Ad-Tech ECOG strip has been classified as non-significant risk devices by the UAB IRB in another protocol. Minimally invasive ECOG recordings are used routinely worldwide to localize seizures and for brain mapping. They have been used locally by multiple neurosurgeons at UAB over a period of decades. Because patients in this protocol are undergoing DBS surgery as part of routine care, the hole in the skull and the penetration of the DBS through the outer layer of the brain (the dura) occurs regardless of whether the research is conducted. Therefore, the only incremental risk relates to the placement of the flexible ECOG strip in the subdural space posterior to the hole in the skull. For the proposed research, we use ECOG strips to measure how deep brain stimulation (DBS) changes cortical activation patterns. This approach to DBS physiology has been developed by Phil Starr, MD, PhD at the University of California San Francisco, who has provided publications on feasibility and safety. Other groups

worldwide have begun using ECOG to inform DBS targeting during surgery, as well. The UCSF group has extensive experience temporarily placing these strips in more than 200 DBS patients, and they report no significant adverse events (e.g., no direct cortical damage, change in cortical MRI signal where strip was placed, seizure, or bleeding near the ECOG site). Additionally, Dr. Kristen Riley in the UAB Department of Neurosurgery has implanted hundreds of ECOG strips in epilepsy patients and Dr. Bart Guthrie has implanted ECOG strips in DBS patients as part of other research protocols, and there have been no instances of hemorrhage that damaged brain tissue. Since placement of the sterile ECOG strips is brief and temporary (typically for minutes to hours), the incremental risk of infection is likely negligible.

9. External delivery of electrical stimulus pulses through the implanted DBS electrode array: The MultiChannel Systems STG4000 stimulator has been classified as a non-significant risk device by the UAB IRB in other protocols. The STG4000 contains eight optically isolated biphasic stimulus isolation units that are connected to the patient's existing segmented DBS electrode array during surgery. This increases sync precision and allows us to deliver unique stimulation patterns that are unavailable with the commercial DBS devices currently available in the U.S. Explicit control of the timing of the stimulus also brings us closer to an eventual goal of "real time" analyses in the operating room. The experimental stimuli are delivered through the segmented electrode contacts on the DBS system that has already been implanted as part of routine care. We will still use the Boston Scientific stimulator and their segmented electrode for clinical/behavioral DBS testing in the OR, as per routine.

b. Estimate the frequency, severity, and reversibility of each risk listed.

For this research participants will be assigned a random identification number, which will be linked to the participant's name. The linking document will be stored in a safe kept behind a locked door in the PI's laboratory space in the Sparks Center. In publications or presentations of the data, subjects will not be identified by name. All digital data including camera images of participant's movements will be stored in password protected computers in the PI's laboratory behind a locked door. Hard copies of data will be stored in the same safe described above. We believe the risk for loss of privacy is low.

Two percent of DBS implantation cases under the current standard of care result in infection. Device infection is not life threatening but often requires removing the whole system and repeating the craniotomy from the beginning. During DBS surgeries at UAB the utmost care is placed on maintaining surgical sterility. We always monitor patients closely to detect signs of infection. We view the increased risk because of additional surgical time needed for the research as small and have been granted <30 minutes for research in the OR in prior protocols without a suggestion of higher infection risk. The research protocol does not involve additional surgery or any kind of incremental tissue perturbation beyond routine care. Rather, it involves delivering electrical stimuli and measuring brain rhythms with the patient at rest.

It is unlikely that mechanical problems will be experienced with Boston Scientific's Vercise PC and directional lead at rates greater than those seen with other commercial devices. The device is CE marked for use in Europe and has been in use clinically for some time now in countries such as Germany, the United Kingdom, and Israel. Recent reports in the literature suggest that the device is technically sound. A device that is found to not be working properly may need to be explanted and replaced with a completely new device.

Directional DBS using current steering might not provide therapeutic benefit. This is unlikely as the device is being used in Europe and early studies indicate that stimulation through the

segmented lead is effective in controlling symptoms of Parkinson's disease. However, if it is found that stimulation is ineffective, the segmented device can be programmed like the current commercially available device in a conventional "ring mode" configuration.

Our routine practice is to place unilateral DBS in the most affected side of the brain, followed by contralateral surgery, if and when it is indicated based upon motor symptoms. PD motor symptoms are typically asymmetric with respect to the side of the body that is affected most, and this asymmetry persists lifelong within an individual. The per protocol analysis for our project evaluates unilateral and not bilateral DBS over the first 6 months of therapy, followed by an open label evaluation at a Study Exit visit at 1 year after surgery. We have budgeted the necessary number of devices for contralateral surgery in a subset of participants over the entire 5-year duration of the study, based upon our prior publications in this area35-36 and a review of a large consecutive series from our clinical practice (please see blue trace on the figure above). Based upon these data, we anticipate potentially needing to place contralateral DBS within 6 months of unilateral surgery for the BRAIN Initiative study in <10% of participants. This is likely an overestimate, because we are recruiting participants who understand that we want to avoid the second surgery within the first year if possible and who are on average at an earlier disease stage versus most prior DBS studies.
Similar to other commercially available devices, the Boston Scientific Vercise PC battery has not been, nor will it ever be, declared safe for brain or body MRI. If participants require contralateral DBS for the other side of their brain, lack of MRI on the day of their second surgery could make targeting of the implanted electrode less optimal in some cases if we use CT images for targeting. Risk is mitigated because we can use intraoperative imaging to mirror the location of their other DBS lead to target the opposite side of the brain. Additionally, as part of routine care we have implanted a number of DBS electrodes with CT targeting in patients who have MRI contraindication for other reasons (cardiac pacemakers, spinal cord stimulators, shrapnel in the body from accidents) with good clinical outcomes.
Symptoms related to participants being "off" their dopaminergic medications can be easily alleviated by having them take a dose of their medications. Participants will be instructed to bring their medications with them to the off medication assessments and will be allowed to take them immediately following testing.

Our EEG, ECOG, and external stimulator devices have all been previously classified by the IRB as non-significant risk devices. Thus, we foresee minimal risk with their use.

c. Is this a therapeutic study or intervention? ☒Yes ☐No

If Yes, complete the following items:

i. Describe the standard of care in the setting where the research will be conducted:

A deep brain stimulator (DBS) is a surgically implanted device used to treat several disabling neurological symptoms such as tremor, rigidity, stiffness, slowed movement, and walking problems in persons with Parkinson's disease. DBS is only implanted in patients that have exhausted all reasonable attempts at drug control for their symptoms. The device consists of two components, the stimulating electrode, which is implanted in the brain, and an implanted pulse generator (IPG) that is implanted in the chest wall, similar to a heart pacemaker.

Prior to surgery each patient is evaluated by a multidisciplinary team to assess the patient's candidacy for surgery. At UAB, DBS surgery is conducted in two stages. Prior to stage one, patients receive an MRI scan to aid in neurosurgical targeting. A small burr hole is made in the skull and the stimulating electrode is moved to the surgical target aided by the use of

microelectrode recordings. When the correct anatomical location is reached, the DBS is turned on and a neurologist assesses tolerability and ensures that no motor side effects from stimulation are present. The wire is then coiled under the scalp and the patient is sewn up. Post-operative MRI ensures the correct positioning of the DBS electrode. Patients return one week later to have the IPG placed in the chest. At this time the previously coiled wire is tunneled down the neck under the skin and to the chest where it is attached to the IPG.

Roughly one month later patients are seen in clinic to have their device turned on. Each stimulation contact is tested using monopolar stimulation and thresholds for side effects are measured. Patients have their device programmed at settings that alleviate symptoms and avoid side effects. Patients then return after three months to be reassessed. Following this visit patients are generally seen once every six months or as needed. DBS does often reduce the amount of dopaminergic drugs that are needed, but continual drug therapy is typically needed in conjunction with DBS for optimum Parkinsonian symptom relief.

ii. Describe any other alternative treatments or interventions:

DBS is an elective procedure done as part of routine care. Alternative treatments include not participating in the study and being implanted with the device that is currently commercially available instead or to not have a DBS device implanted at all. Patients choosing the latter would continue only with drug therapy for control of their Parkinson's symptoms.

iii. Describe any withholding of, delay in, or washout period for standard of care or alternative treatment that participants may be currently using:

We will ask our participants to delay taking their Parkinson's medications prior to each clinical visit. We are interested in testing the effects of the brain stimulator alone and in order to adequately assess this, our participants need to be in the clinically defined "off" medication state.

d. Do you foresee that participants might need additional medical or psychological resources as a result of the research procedures/interventions? ☐Yes ☒No
If Yes, describe the provisions that have been made to make these resources available.

_____

e. Do the benefits or knowledge to be gained outweigh the risks to participants?
☒Yes ☐No

If No, provide justification for performing the research:_____

19. Precautions/Minimization of Risks

a. Describe precautions that will be taken to avoid risks and the means for monitoring to detect risks.

1. **Loss of privacy: Information obtained about patients will be kept private to the extent allowed by law. Identifying information may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research. Each participant will be assigned a randomly generated identification number. All information and data will be grouped by identification number which is linked to participant name in a linking document. This linking document will be kept in a locked safe behind a locked door in the PI's laboratory space in the Sparks Center. In publications or presentations**

of the data, subjects will not be identified by name. All digital data including camera images of participant's movements will be stored in password protected computers in the PI's laboratory behind a locked door. Hard copies of data will be kept in the same safe described above.

2. Physical risks related to the surgical procedure: Participation in this research will not alter routine clinical care in any way, except that the surgery will last from 0 to 30 minutes longer than routine care. We design our studies to last around 20 minutes or less, however we have IRB approval for 30 minutes beyond routine care. Our research stimulation protocol is almost completely computer-driven, which further minimizes additional time during surgery. Additionally, we can often incorporate research time into pauses in the procedure that occur as part of routine care. To the extent that it is possible, we avoid behavioral testing in the operating room solely for research purposes, because the awake craniotomy can be a stressful experience for patients. Detailed behavioral measures are instead obtained in the context of study visits or routine care, as this is a more natural environment with fewer time constraints. At present, the results of our research are not analyzed in real time and therefore cannot influence routine care. Despite their promise, we are cognizant that the proposed biomarkers or other aspects of our approach could inadvertently do harm. We therefore would not use real time analyses of the intraoperative physiology to alter routine care without more extensive validation in prospective studies. Protection from surgical and medical risks will otherwise be identical to non-study patients undergoing DBS therapy. This includes routine practices such as preoperative prophylactic antibiotics, strict control of blood pressure during surgery, and verification of normal preoperative coagulation studies.

3. Boston Scientific Vercise PC and Directional Lead. With commercial DBS devices, there can be various forms of mechanical and/or electrical failure, including battery leakage, battery failure, lead or extension breakage, hardware malfunctions, loose connections, electrical shorts or open circuits, and lead insulation breaches. These potential failures may require various levels of surgical revision, including potentially revision of the entire system including craniotomy. Whether these kinds of issues are more or less common with the Boston Scientific device is unclear. Patients will be asked to report to their physician any of the following symptoms immediately:
   a) Allergic or immune system response to implanted materials
   b) Implant site complications such as pain, poor healing, redness, warmth, swelling or wound reopening
   c) Implanted device components (stimulator, lead or extension) moving from original implanted location or wear through the skin
   d) Infection
   e) Interference from external electromagnetic sources
   f) Loss of adequate stimulation
   g) Pain, headache, or discomfort
   h) Skin irritation or burns at the stimulator site
   i) Stiffness in muscles or with joint movement
   j) Sudden return of symptoms, if stimulation is stopped abruptly. In Parkinson's disease, there have been rare cases of rapid symptom return progressing to inability to move.
   k) Swelling, including fluid collecting around the device.

   Note that some of these symptoms may be resolved or reduced by current steering, changing stimulation parameters, or by changing the position of the lead during surgery.

4. Directional brain stimulation. Commercially available DBS leads in the US consist of a linear array of ring-shaped electrodes. We are studying segmented leads developed by Boston Scientific to steer current and better optimize DBS efficacy and tolerability in individuals. Evidence from recent studies in Europe by Timmermann et al and Volkmann et al suggest that this current steering approach is feasible for these purposes, however it is possible that the activation of individual segments alone will not provide therapeutic benefit or that they will not improve the thresholds for potential side effects from DBS in individual patients. If this were the case, we can still activate all three segments simultaneously so that the individual segments act together as a traditional ring electrode. In this respect, we will have access to routine DBS settings either acutely or long-term, if they are needed or preferred by individual participants.

5. MRI compatibility of Boston Scientific Vercise PC Implanted Pulse Generator: We have at least 3 contingencies to address this potential situation. First, we anticipate having access to intraoperative MRI at UAB by early 2019 (the OR suite with intraoperative MRI is currently under construction in the Women's and Children's Center). With intraoperative MRI, we could remove the Vercise PC battery, perform MRI in the OR, implant the new DBS lead for the second side, and then connect both the new and old extension wires to the Vercise Pbattery in a single procedure. Second, if intraoperative MRI is unavailable at UAB when the participant elects to undergo staged DBS for the other side of the brain, an additional brief surgery could be performed to remove the MRI incompatible Vercise PC battery, followed by MRI and implant of the new DBS lead, and then replacement of the battery. Third, the patient and care team could elect to do targeting for the second DBS surgery with CT instead of MRI. Although we have successfully placed DBS leads with CT guidance as part of routine care for numerous patients with other contraindications for MRI (i.e., pacemakers, spinal cord stimulators, other implanted devices), CT imaging alone might be less accurate than MRI for lead targeting in some individuals.

6. "Off" medication assessments. To minimize travel and expense for participants, research studies in the Neuromechanics Laboratory are arranged on days when participants would be scheduled for follow-up appointments whenever possible, and the relevant clinical outcomes are obtained as part of routine care visits. Being "off" dopaminergic medications can temporarily cause the return of Parkinsonian symptoms. DBS patients routinely arrive for clinic evaluations "off" their dopaminergic medications, both as part of DBS surgery and stimulation adjustments for routine care. While uncomfortable for some patients, these "off" meds assessments are a standard practice for participation in surgical trials for PD. Any symptoms participants experience can be easily reversed by taking the next scheduled dose of medication.

7. Electroencephalography (EEG): For intraoperative EEG studies, patients wear one of nine specially made caps, six of which allow space for the sterile field on the scalp that is required for either right or left craniotomy. Active electrode technology and the cap itself make application of the EEG electrodes faster and less invasive than traditional EEG electrodes because the recording sites on the scalp do not have to be rubbed vigorously with an alcohol pad, and electrode locations do not have to be individually measured on the skull. Both the caps and EEG electrodes are disinfected after each use. The most significant risk of our studies with respect to EEG is discomfort associated with having standard conductive gel in the patient's hair (small amounts injected between the scalp and each EEG electrode). The EEG signal is acquired onto a high performance laptop computer that is not connected to the wall outlet.

8. Electrocorticography (ECOG): The Ad-Tech ECOG electrodes are made of a rubbery material and are thin, smooth, and flexible. This pliable design is explicitly to avoid tissue penetration of any kind. The ECOG electrodes are placed in the subdural space and passively record activity

from the outer surface of the brain. We have used ECOG in DBS patients under a different protocol with no subjective or objective adverse consequences. In contrast to ECOG in epilepsy patients, we will only place a single strip (in epilepsy cases, it is routine to pass multiple electrode strips and/or larger grids), therefore our approach is less invasive than routine care for patients with epilepsy. Additionally, the UCSF group has implanted ECOG in dozens of movement disorders patients undergoing DBS surgery without significant adverse events. Closely following their methods, we will avoid ECOG strips in patients with significant brain atrophy (shrinkage), and we will use imaging guidance during placement to make sure the strip isn't "folding." We will abort the study if passing the ECOG strip encounters any physical resistance whatsoever. Although there is a theoretical risk for infection, as above, the ECOG strips in these studies are only implanted temporarily.

9. External delivery of electrical pulses through the DBS wire with the MultiChannel STG 4000 stimulator: Prior to any use of the STG4000 in human subjects, we connected it to an externalized Medtronic DBS lead in the lab. This lead was connected to a resistor approximating the resistance of the human brain tissue (2 kOhms), and an oscilloscope verified the amplitude and timing of the stimulus pulse when compared to that of the commercial device. Potential risks of using the STG4000 in this protocol are minimal for the following reasons:
   a. This is a research protocol. The results of the ERP assay do not alter surgical care or decision-making, and the STG4000 is only used temporarily.
   b. The proposed studies only deliver single pulses with narrow pulse widths (~60 to 120 microseconds), and we do not deliver chronic, continuous stimulation at greater than 100 pulses per second over a period of years or even decades (as occurs with routine clinical care).
   c. Stimulus intensity will always be well within the established safety limits for electrical stimulation of neuronal tissue mandated by the FDA (less than 30 μcoulombs/cm^2/phase, a conservative estimate of the amount of charge delivery that could cause irreversible damage to human nervous tissues).
   d. We always verify normal tissue impedance with the impedance testing function prior to any experimental stimulation. Additionally we use the therapeutic impedance measurement to convert the stimulation voltage to its corresponding constant current value with the external stimulator. This ensures that the current delivered during this experiment is never greater than the FDA-mandated limit from item 4.c. above.
   e. Each stimulus pulse is charge-balanced, such that there is no net delivery of charge into the brain.
   f. Our stimulus isolation units are optically isolated and powered by detachable batteries, such that there is no electrical connection between the wall outlet and the neural tissue of the participant. There is no risk for a power surge from the electrical outlet entering the brain of a participant.
   g. The PI stimulated himself with an externalized DBS electrode connected to both the commercial DBS and the STG4000 stimulator to verify that identical threshold stimulation parameters elicited tingling of the skin.
   h. This external stimulator system has been used on numerous patients in other protocols without subjective or objective adverse consequences.
   i. The investigators have extensive experience with DBS programming and surgery. Consequently, we are well-positioned to provide safety monitoring in real time.
   j. As a part of routine care, we always increase stimulation parameters (amplitude, frequency, and pulse width) cautiously from lower to higher stimulation intensities in DBS patients. Experienced neurology and neurosurgery personnel are present at all times during the research protocol. In the unlikely circumstance where the patient experiences discomfort,

we immediately deactivate the stimulation device, as we would do during routine care of patients with a brain stimulator.

k. **Our collaborator Arie Nakhmani, PhD, from UAB Electrical Engineering, provides input on safety and technical issues with all peripheral devices.**

l. **We will verify the safety of the MultiChannel STG4000 stimulation unit with a yearly on-site biomedical engineering safety check.**

10. **At the end of each year a safety monitoring committee will convene to discuss all study related AEs and SAEs and to ensure the ongoing safety of the study. The safety monitoring committee will include:**

Elizabeth Zauber, MD, Associate Professor of Neurology, IUPUI, szauber@iupui.edu,

Kristen Riley, MD, Associate Professor of Neurosurgery, UAB, kriley@uab.edu, and

George Howard, PhD, Professor of Biostatistics, UAB, ghoward@uab.edu.

If study involves drugs or devices skip Items 19.b. and 19.c., go to Item 20, and complete the Drug or Device Review Sheet, as applicable.

b. If hazards to an individual participant occur, describe (i) the criteria that will be used to decide whether that participant should be removed from the study; (ii) the procedure for removing such participants when necessary to protect their rights and welfare; and (iii) any special procedures, precautions, or follow-up that will be used to ensure the safety of other currently enrolled participants.

---

c. If hazards occur that might make the risks of participation outweigh the benefits for all participants, describe (i) the criteria that will be used to stop or end the entire study and (ii) any special procedures, precautions, or follow-up that will be used to ensure the safety of currently enrolled participants.

---

20. Informed Consent

a. Do you plan to obtain informed consent for this protocol? ☒Yes ☐No
If Yes, complete the items below.
If No, complete and include the Waiver of Informed Consent or Waiver of Authorization and Informed Consent, as applicable.

b. Do you plan to document informed consent for this protocol? ☒Yes ☐No
If Yes, complete the items below.
If No, complete the items below **and** include the Waiver of Informed Consent Documentation.

c. How will consent be obtained?

Study personnel with consenting privileges will discuss the study details with eligible participants previously identified through a review of clinic records. If the patient is interested, an informed consent discussion will be conducted and an informed consent form will be signed. All conversations regarding the study will be held in a private setting such as a clinic room or physician's office.

d. Who will conduct the consent interview?

The PI or study personnel as listed in 3.

e. Who are the persons who will provide consent or permission?

The study participant

f. What steps will be taken to minimize the possibility of coercion or undue influence?

Potential subjects will be informed of risks and benefits, informed about voluntary participation and it will be emphasized that their participation will in no way affect their routine care.

g. What language will the prospective participant or the legally authorized representative understand?
English.

h. What language will be used to obtain consent?

English.

i. If any potential participants will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process, describe the precautions proposed to overcome the effect of the condition on the consent process. If not, enter "no such effect."

No such effect.

j. If any project-specific instruments will be used in the consenting process, such as flip charts or videos, describe the instrument(s) here, and provide a copy of each. If not, enter "not used."

Not used.

k. How long will participants have between the time they are told about the study and the time they must decide whether to enroll? If not 24 hours or more, describe the proposed time interval and why the 24-hour minimum is neither feasible nor practical.

At least 24 hours.

21. Procedures to Protect Privacy

Describe the provisions included in the research to protect the privacy interests of participants (e.g., others will not overhear your conversation with potential participants, individuals will not be publicly identified or embarrassed).

Recruitment of potential subjects will be conducted behind closed doors in TKC during clinic visits in an effort to minimize the ability of others to overhear these conversations. Research visits will be conducted individually and not in a group setting. Individuals will not be publicly identified or embarrassed.

22. Procedures to Maintain Confidentiality

a. Describe the manner and method for storing research data and maintaining confidentiality. If data will be stored electronically anywhere other than a server maintained centrally by UAB, identify the departmental and all computer systems used to store protocol-related data, and describe how access to that data will be limited to those with a need to know.

All participant information will be coded with an assigned participant identification number, and study forms will not contain any other individually identifying information. All information and data will be grouped by identification number which is linked to participant name in a linking document. This linking document will be kept in a locked safe behind a locked door in the PI's laboratory space in the Sparks Center. In publications or presentations of the data, subjects will not be identified by name. All digital data including camera images of participant's movements will be stored in password protected computers in the PI's laboratory behind a locked door. Hard copies of data will be kept in the same safe described above.

b. Will any information derived from this study be given to any person, including the subject, or any group, including coordinating centers and sponsors? ☒Yes ☐No

If Yes, complete i-iii.

i. To whom will the information be given? **Study sponsor, Boston Scientific.**

ii. What is the nature of the information? **progress reports**

iii. How will the information be identified, coded, etc.? **All data we provide will include only patient ID, device serial numbers, or other device related information.**

23. Additional Information

In the space below, provide any additional information that you believe may help the IRB review the proposed research, or enter "None."

We have attached the relevant device review sheets, the original grant application including the protocol synopsis, preliminary findings and aims, and the study milestones approved by officials at the NIH.

Year 1

Milestone 1.1:	**Join and maintain active membership status in NIH-coordinated data sharing consortium.**
Success Criteria:	Actively participate in the data sharing consortium, and adopt best practices/efforts to comply with the recommendations of the data sharing consortium, throughout all years and/or stages of the award.
Rationale:	Participation and maintaining an active membership status in the consortium is a requirement of the RFA.
Milestone 1.2:	**Obtain FDA IDE for the use of the Boston Scientific Vercise DBS system with their novel directional lead.**

Success Criteria: A full approval letter from FDA, obtained in collaboration with Boston Scientific, with no major study design considerations. A copy of the FDA approval letter will be sent to the NIH Project Officer. All correspondence from FDA regarding the IDE will be shared with the NIH Project Officer within 30 days of receipt.

Rationale: The IDE is required for study initiation. Boston Scientific's regulatory staff estimates that the IDE can be obtained within 6 to 9 months. Any major study design consideration will be considered and resolved to maximize the probability that a future pivotal study can proceed with the data collected in this feasibility study.

Milestone 1.3: **Obtain IRB approvals of final clinical study as approved by FDA and register the study on www.clinicaltrials.gov.**

Success Criteria: Documentation of full approval from the UAB IRB, along with registration on clinicaltrials.gov. IRB approval and informed consent documents will be shared with the NIH Project Officer.

Rationale: Maintaining IRB approval is a requirement for a clinical study as is registering the study on www.clinicaltrials.gov.

Milestone 1.4: **Safety Monitoring Committee will meet to discuss all AEs and SAEs at the end of Y1.**

Success Criteria: The SMC will include a biostatistician, and neurosurgeon, and a neurologist. Meeting proceedings and decisions will be communicated to the PI and to the NIH Project Officer.

Rationale: This process will ensure ongoing safety of the study.

Milestone 1.5: **Participant enrollment follows approved protocol.**

Success Criteria: All subjects follow research protocol as summarized in **Error! Reference source not found.** and **Error! Reference source not found.**. Follow-up at 1 year post-crossover completion with ≥80% of the participants.

Rationale: Overall randomization and study design has been approved by NIH staff. As this is a deviation from what was originally in the proposal, this new study design should be followed. All further deviations should be negotiated and approved by NIH prior to changes being made.

Milestone 1.6: **Form Scientific Steering Group and hold a meeting to review project status, problems and direction.**

Success Criteria: Meeting participants, proceedings and decision(s) will be communicated to NIH program staff.

Rationale: This is a requirement of the RFA and will help to ensure continued progress and success of the project.

Milestone 1.7: **Review IRB and IDE paperwork to ensure both are up to date and allow for a sufficient scope and number of subjects for successful completion of work proposed in the upcoming year.**

Success Criteria: Confirm paperwork is up to date and NINDS staff has the most recent version.

Rationale: Maintaining IRB and IDE approval is a requirement for a clinical study.

Year 2

Milestone 2.1: **Maintain active membership status in NIH-coordinated data sharing consortium.**

Success Criteria: Actively participate in the data sharing consortium, and adopt best practices/efforts and comply with the recommendations of the data sharing consortium, throughout all years and/or stages of the award.

Rationale: Participation and maintaining an active membership status in the consortium is a requirement of the RFA.

Milestone 2.2: **Complete the pre-operative assessment battery and implant the Boston Scientific Vercise DBS system with the directional lead in at least 12 participants by the end of Y2.**

Success Criteria: Successfully implant the Vercise DBS system with directional lead, extension cable, and pulse generator in 12 participants using standard STN stereotaxy. Successful implant is defined as placement of the entire DBS system without surgical adverse events (such as stroke, infection, seizure) or any other adverse event that prevents postoperative device activation, adjustment, and/or behavioral testing. Results will be recorded in a surgical implantation document form including system tests showing normal DBS electrode impedances and typical behavioral responses during test stimulation in surgery (i.e., side effect and efficacy thresholds). These data will be summarized at the time the yearly annual report for Y2 is submitted.

Rationale: Our goal to implant 12 (or more) participants by the end of Y2 will enable initial follow-up and randomization in these participants during Y2 and Y3. Based on our clinical volume and experience in past studies, we can typically recruit 1 to 3 patients per month who are undergoing STN DBS for PD.

Milestone 2.3: **Acquire and analyze intraoperative cortical physiology during surgery in the initial 12 participants from Milestone 2.2:.**

Success Criteria: Demonstrate delivery of the experimental stimuli through the directional lead during surgery, removal of the stimulus artifact (≥85% amplitude reduction) in EEG and ECOG channels in ≥80% or 10/12 of participants, and measurement of event related potential (ERP) waveforms (with latency and amplitude measurements from both P1/N1 and HFO responses in ≥75% or 9/12 of participants), as shown in our prior publications and pilot data (proposal **Figs. 2-5**). These data will show feasibility for SA 1.2. We will co-register intraoperative O-arm CT images with pre-op brain MRI to localize ECoG, EEG, and DBS contacts.

Rationale: In this first-in-human approach, we will measure patient-specific cortical activation patterns elicited by directional DBS with simultaneous EEG/ECoG. Our goal is to use these methods to optimize and expedite field shaping with novel directional DBS lead technology.

Milestone 2.4: **Determine whether current steering alters the therapeutic window within individual participants during initial device activation in the Monopolar Survey (SA 1.1).**

Success Criteria: Demonstrate ≥20% increase in therapeutic window in at least one electrode contact segment versus conventional omnidirectional DBS ("ring mode") in ≥40% of the participants who have completed the monopolar survey by the end of Y2. Additionally, we will classify all stimulation side effects by type (i.e., motor, sensory, oculomotor, ataxia, autonomic, etc.). To maintain blinding, patients will not be told which survey is being performed or which treatment condition they will receive.

Rationale: Measured routinely in the monopolar survey, therapeutic window is defined as the current difference between the thresholds for efficacy and adverse stimulation effects for each contact on the DBS electrode array. One goal of directional DBS is to increase the size of the therapeutic window versus omnidirectional stimulation within individuals. Based on multiple publications, directional DBS is very likely to accomplish this. Using the criteria proposed above, Stiegerwald et al recently showed a 31% median improvement in therapeutic window and greater than 20% improvement in at least one contact in 9 of 11 patients (81%). Based on their data, we believe that our 40% success criterion is conservative, not only relative to their early results, but also given that improvement in 40% of patients (or even less) might still be a clinically important difference. In an unlikely scenario where there is no change in the floor of the therapeutic window, or it occurs relatively infrequently (in <40% of participants), we could still proceed with the randomized crossover, as proposed in SA2.3, instead selecting contacts based on therapeutic window size or percent change in UPDRS subscore for the stimulated side of the body, rather than therapeutic window floor. Field shaping with multiple active contacts on the novel DBS lead still might be preferred by patients based on activating larger tissue volumes in the STN region, regardless of whether directional stimulation alters therapeutic window floor. This option would be discussed and negotiated with NIH staff to explore this possibility based on the available data at the time.

Milestone 2.5: **Characterize changes in ERPs measured by EEG/ECoG with directional stimulation during DBS surgery.**

Success Criteria: We propose that current steering with the directional lead will yield within-participant changes in ERPs that mirror the EEG findings with omnidirectional DBS in our Supporting Data (proposal **Figs. 2-5**). Specifically, we anticipate that contacts with large therapeutic windows will display P1/N1 peak latencies of ≥550 μsec (proposal **Fig. 3D**) and absence of the large amplitude HFO (proposal **Fig. 4C**). Conversely, we anticipate that contacts with small therapeutic windows will display P1/N1 latencies of <550 μsec and presence of the HFO. In addition to these criteria, we will also investigate whether directional stimulation alters the spatial distribution of ERP responses on the ECoG strip. Criteria for success are to demonstrate that directional stimulation yields similar quantitative changes in ERP timing and morphology within individuals.

Rationale: This milestone focuses on feasibility of using the intraoperative EEG/ECoG assay to inform the use of directional DBS technology. Initial goals are to demonstrate that directional DBS can yield within-participant changes in ERP latency, morphology, localization and other parameters with EEG/ECoG that predict behavioral responses to stimulation (SA 1.2).

Milestone 2.6: **Determine whether patient-specific *combinations* of active DBS contact segments, guided by cortical physiology versus behavior alone, acutely modify the therapeutic window during the Field Shaping Survey (SAs 2.1 and 2.2).**

Success Criteria: Demonstrate significant changes in the therapeutic window with field shaping within individuals, defined as ≥20% improvement or worsening therapeutic window in at least one grouping of 3 electrode contact segments versus omnidirectional DBS in ≥40% of the participants who have reached the Field Shaping Survey by the end of Y2. We will rank each of the 8 contact segments for their likelihood for efficacy (SA2.1) and motor side effects (SA2.2), based on quantitative behavioral and cortical physiology criteria. We will simultaneously activate the 3 most highly ranked contact segments for behavioral testing with effective versus adverse combinations of contacts (SAs 2.1 versus 2.2), based on these criteria. The survey will be performed in conjunction with the assessment battery after the second treatment phase. To maintain blinding, patients will not be told which survey is being performed or which treatment condition they will receive.

Rationale: In this first-in-human approach, we will reversibly activate unique combinations of DBS contact segments, guided by cortical physiology and behavioral criteria, to explore putative biomarkers to guide field shaping with multiple directional DBS contacts. This dose-finding and safety study will directly inform contact selection for the final arm of the double-blind crossover and other related milestones.

Behavioral criteria for contact selection in SA2.1 arise from the Monopolar Survey and will be defined as the 3 lead segments with the lowest floor of the therapeutic window. As previously, if we were unable to demonstrate changes in therapeutic window floor with directional DBS either at the individual or group level in Milestone 2.4:, we would instead use the three contacts that displayed the greatest therapeutic window magnitude or percent improvement in UPDRS hemibody subscore for the stimulated side of the body. Behavioral criteria for contact selection in SA2.2 will be defined as the 3 lead segments with the lowest (worst) stimulus amplitude thresholds for adverse capsular motor side effects (involuntary contraction of the mouth, arm, or leg).

Cortical physiology criteria for contact selection in SA2.1 arise from analyses of intraoperative EEG/ECoG studies in Milestone 2.3:. We have previously demonstrated that within-participant changes in P1/N1 amplitude are associated with the magnitude of improvement in motor symptoms during high frequency DBS for PD and essential tremor. Thus, EEG criteria for contact selection in SA2.1 are peak latency of ≥550 μsec (proposal **Fig. 3D**) and absence of the large amplitude HFO (proposal **Fig. 4C**). We will rank and simultaneously activate the 3 most promising lead segments that meet the above criteria based upon P1/N1 peak amplitude. The EEG criteria for SA2.2 are P1/N1 latency <550 μsec (proposal **Fig. 3D**) and presence of the HFO (proposal **Fig. 4C**). We will then rank and simultaneously activate the 3 lead segments based upon P1/N1 peak amplitude. In addition to these criteria, we will also investigate whether directional stimulation alters the spatial distribution of ERP responses on the ECoG strip.

Milestone 2.7: **Establish cognitive and behavioral safety related to directional versus omnidirectional DBS.**

Success Criteria: No more than 2 patients experience worsening on more than 30% of the test scores as quantified as more than a 1.5 standard deviation score decline beyond any identified level of change, as reported from the DBS surgery literature.

Rationale: Although conventional bilateral STN DBS is safe cognitively and behaviorally at the group level, an important goal is to identify potential changes related to the field shaping approach; we are positioned to sensitively detect these changes within subjects, should they occur. If risks are identified that are beyond those reported in the literature, conventional DBS in ring mode is still available.

Milestone 2.8: **Safety Monitoring Committee will meet to discuss all AEs and SAEs at the end of Y2.** This committee will also meet on an as-needed basis following SAEs to determine whether they are study-related versus a known complication of DBS surgery.

Success Criteria: Meeting proceedings and decisions will be communicated to the PI and NINDS program officers.

Rationale: This process will ensure ongoing safety of the study

Milestone 2.9: **Participant enrollment follows approved protocol.**

Success Criteria: All subjects follow research protocol as summarized in **Error! Reference source not found.** and **Error! Reference source not found.**. Follow-up at 1 year post-crossover completion with ≥80% of the participants.

Rationale: Overall randomization and study design has been approved by NIH staff. As this is a deviation from what was originally in the proposal, this new study design should be followed. All further deviations should be negotiated and approved by NIH prior to changes being made.

Milestone 2.10: **Hold a Scientific Steering Group meeting to review project status, problems and direction.**

Success Criteria: Meeting participants, proceedings and decision(s) will be communicated to NIH program staff.

Rationale: This is a requirement of the RFA and will help to ensure continued progress and success of the project.

Milestone 2.11: **Review IRB and IDE paperwork to ensure both are up to date and allow for a sufficient scope and number of subjects for successful completion of work proposed in the upcoming year.**

Success Criteria: Confirm paperwork is up to date and NINDS staff has the most recent version.

Rationale: Maintaining IRB and IDE approval is a requirement for a clinical study.

Year 3

Milestone 3.1: **Maintain active membership status in NIH-coordinated data sharing consortium.**

Success Criteria: Actively participate in the data sharing consortium, and adopt best practices/efforts to comply with the recommendations of the data sharing consortium, throughout all years and/or stages of the award.

Rationale: Participation and maintaining an active membership status in the consortium is a requirement of the RFA.

Milestone 3.2: **Complete the pre-operative assessment battery and implant the Boston Scientific Vercise DBS system with the directional lead in 15 additional participants in Y3, for a total of at least 27 enrolled and implanted participants.**

Success Criteria: Successfully implant the Vercise DBS system with directional lead, extension cable, and pulse generator in 15 participants using standard STN stereotaxy. Successful implant is defined as placement of the entire DBS system without surgical adverse events (such as stroke, infection, seizure) or any other adverse event that prevents postoperative device activation, adjustment, and/or behavioral testing. Results will be recorded in a surgical implantation document including system tests showing normal DBS electrode impedances and side effect and efficacy thresholds during test stimulation. These data will be provided to NIH. To maintain blinding, patients will not be told which survey is being performed or which treatment condition they will receive.

Rationale: This is a minimum requirement to reach target of 27 participants implanted by the end of Y3 and will enable initial follow-up and randomization to be completed in these patients by Year 4.

Milestone 3.3: **Safety Monitoring Committee will meet to discuss all AEs and SAEs at the end of Y3.** This committee will also meet on an as-needed basis following SAEs to determine whether they are potentially study-related versus a known complication of DBS surgery.

Success Criteria: Meeting proceedings and decisions will be communicated to the PI and NINDS program officers.

Rationale: This process will ensure ongoing safety of the study.

Milestone 3.4: **Hold a Scientific Steering Group meeting to review project status, problems and direction.**

Success Criteria: Meeting participants, proceedings and decision(s) will be communicated to NIH program staff.

Rationale: This is a requirement of the RFA and will help to ensure continued progress and success of the project.

Milestone 3.5: **Participant enrollment follows approved protocol.**

Success Criteria: All subjects follow research protocol as summarized in **Error! Reference source not found.** and **Error! Reference source not found.**. Follow-up at 1 year post-crossover completion with ≥80% of the participants.

Rationale: Overall randomization and study design has been approved by NIH staff. As this is a deviation from what was originally in the proposal, this new study design should be followed. All further deviations should be negotiated and approved by NIH prior to changes being made.

Milestone 3.6: **Review IRB and IDE paperwork to ensure both are up to date and allow for a sufficient scope and number of subjects for successful completion of work proposed in the upcoming year.**

Success Criteria: Confirm paperwork is up to date and NINDS staff has the most recent version.

Rationale: Maintaining IRB and IDE approval is a requirement for a clinical study.

Year 4

Milestone 4.1: **Maintain active membership status in NIH-coordinated data sharing consortium.**

Success Criteria: Actively participate in the data sharing consortium, and adopt best practices/efforts to comply with the recommendations of the data sharing consortium, throughout all years and/or stages of the award.

Rationale: Participation and maintaining an active membership status in the consortium is a requirement of the RFA.

Milestone 4.2: **Complete the pre-operative assessment battery and implant the Boston Scientific Vercise DBS system with the directional lead in at least 3 additional participants in Y4, for a total of at least 30 enrolled and implanted participants.**

Success Criteria: Successfully implant the Vercise DBS system with directional lead, extension cable, and pulse generator in 3 participants using standard STN stereotaxy. Successful implant is defined as placement of the entire DBS system without surgical adverse events (such as stroke, infection, seizure) or any other adverse event that prevents postoperative device activation, adjustment,

and/or behavioral testing. Depending on potential attrition and AEs, this modest recruitment goal for early Y4 will provide flexibility to recruit additional participants to reach our goal of 30 participants for randomization, if necessary. Results will be recorded in a surgical implantation document including system tests showing normal DBS electrode impedances and side effect and efficacy thresholds during test stimulation. These data will be provided to NIH. To maintain blinding, patients will not be told which survey is being performed or which treatment condition they will receive.

Rationale: This is a minimum requirement to reach target of 30 participants implanted and randomized in the crossover by the end of Year 4 and will enable initial follow-up to be completed by Year 5.

Milestone 4.3: **Demonstrate changes in the therapeutic window using directional DBS and field shaping, guided by cortical activation patterns elicited by DBS during surgery (SAs 1.1, 1.2, 2.1, and 2.2).**

Success Criteria: Guided by cortical physiology elicited by DBS, demonstrate ≥20% increase in therapeutic window in at least one grouping of 3 contact segments versus omnidirectional DBS in ≥40% of the participants who have completed the field shaping survey by the end of Year 4. As per Milestone 2.4, we will classify all stimulation side effects by type (i.e., motor, sensory, oculomotor, ataxia, autonomic, etc.). The field shaping survey will be performed in conjunction with the assessment battery after the second treatment phase. To maintain blinding, patients will not be told which survey is being performed or which treatment condition they will receive.

Rationale: The Field shaping survey will evaluate the feasibility of using ECoG/EEG biomarkers to guide directional DBS activation and initiate the final crossover condition. This is a unique dataset that will link simultaneous EEG/ECoG activity elicited by directional DBS with the behavioral response to stimulation.

Milestone 4.4: **Safety Monitoring Committee will meet to discuss all AEs and SAEs at the end of Year 4.** This committee will also meet on an as-needed basis following SAEs to determine whether they are potentially study-related versus a known complication of DBS surgery.

Success Criteria: Meeting proceedings and decisions will be communicated to the PI and NINDS program officers.

Rationale: This process will ensure ongoing safety of the study.

Milestone 4.5: **Participant enrollment follows approved protocol.**

Success Criteria: All subjects follow research protocol as summarized in **Error! Reference source not found.** and **Error! Reference source not found.**. Follow-up at 1 year post-crossover completion with ≥80% of the participants.

Rationale: Overall randomization and study design has been approved by NIH staff. As this is a deviation from what was originally in the proposal, this new study design should be followed. All further deviations should be negotiated and approved by NIH prior to changes being made.

Milestone 4.6: **Hold a Scientific Steering Group meeting to review project status, problems and direction.**

Success Criteria: Meeting participants, proceedings and decision(s) will be communicated to NIH program staff.

Rationale: This is a requirement of the RFA and will help to ensure continued progress and success of the project.

Milestone 4.7: **Review IRB and IDE paperwork to ensure both are up to date and allow for a sufficient scope and number of subjects for successful completion of work proposed in the upcoming year.**

Success Criteria: Confirm paperwork is up to date and NINDS staff has the most recent version.

Rationale: Maintaining IRB and IDE approval is a requirement for a clinical study.

Year 5

Milestone 5.1: **Maintain active membership status in NIH-coordinated data sharing consortium.**

Success Criteria: Actively participate in the data sharing consortium, and adopt best practices/efforts to comply with the recommendations of the data sharing consortium, throughout all years and/or stages of the award.

Rationale: Participation and maintaining an active membership status in the consortium is a requirement of the RFA.

Milestone 5.2: **Participant enrollment follows approved protocol.**

Success Criteria: All subjects follow research protocol as summarized in **Error! Reference source not found.** and **Error! Reference source not found.**. Follow-up at 1 year post-crossover completion with ≥80% of the participants.

Rationale: Overall randomization and study design has been approved by NIH staff. As this is a deviation from what was originally in the proposal, this new study design should be followed. All further deviations should be negotiated and approved by NIH prior to changes being made.

Milestone 5.3: **Hold a Scientific Steering Group meeting to review project status, problems and direction.**

Success Criteria: Meeting participants, proceedings and decision(s) will be communicated to NIH program staff.

Rationale: This is a requirement of the RFA and will help to ensure continued progress and success of the project.

Milestone 5.4: **Safety Monitoring Committee will meet to discuss all AEs and SAEs at the end of Year 5.** This committee will also meet on an as-needed basis following SAEs to determine whether they are potentially study-related versus a known complication of DBS surgery.

Success Criteria: Meeting proceedings and decisions will be communicated to the PI and NINDS program officers.

Rationale: This process will ensure ongoing safety of the study.

Milestone 5.5: **Data entered on clinicaltrials.gov is reviewed by federal interagency staff. Any issues raised during review are resolved by study statistician and data is re-entered accordingly.**

Success Criteria: Data is released to the public via clinicaltrials.gov.

Rationale: Compliance with data reporting requirements.

References:

1. Walker HC, Huang H, Gonzalez CL, et al. Short latency activation of cortex during clinically effective subthalamic deep brain stimulation for parkinson's disease. *Mov Disord.* 2012;27(7):864-873.
2. Walker HC, Huang H, Gonzalez CL, et al. Short latency activation of cortex by clinically effective thalamic brain stimulation for tremor. *Mov Disord.* 2012;27(11):1404-1412.
3. Patel DM, Walker HC, Brooks R, Omar N, Ditty B, Guthrie BL. Adverse events associated with deep brain stimulation for movement disorders: Analysis of 510 consecutive cases. *Neurosurgery.* 2015.
4. Steigerwald F, Muller L, Johannes S, Matthies C, Volkmann J. Directional deep brain stimulation of the subthalamic nucleus: A pilot study using a novel neurostimulation device. *Mov Disord.* 2016.
5. Volkmann J, Chabardes S, Steinke GK, Carcieri S. 375 DIRECT DBS: A prospective, multicenter clinical trial with blinding for a directional deep brain stimulation lead. *Neurosurgery.* 2016;63 Suppl 1:211-212.
6. Reich MM, Steigerwald F, Sawalhe AD, et al. Short pulse width widens the therapeutic window of subthalamic neurostimulation. *Ann Clin Transl Neurol.* 2015;2(4):427-432.
7. Contarino MF, Bour LJ, Verhagen R, et al. Directional steering: A novel approach to deep brain stimulation. *Neurology.* 2014;83(13):1163-1169.
8. Pollo C, Kaelin-Lang A, Oertel MF, et al. Directional deep brain stimulation: An intraoperative double-blind pilot study. *Brain.* 2014;137(Pt 7):2015-2026.
9. Barbe MT, Dembek TA, Becker J, et al. Individualized current-shaping reduces DBS-induced dysarthria in patients with essential tremor. *Neurology.* 2014;82(7):614-619.
10. Nichols AL, Maner JK. The good-subject effect: Investigating participant demand characteristics. *J Gen Psychol.* 2008;135(2):151-165.
11. Schupbach WM, Rau J, Houeto JL, et al. Myths and facts about the EARLYSTIM study. *Mov Disord.* 2014;29(14):1742-1750.
12. Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: Placebo, nocebo, lessebo, and lesion effects. *Mov Disord.* 2016;31(3):290-296.
13. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for parkinson's disease. *N Engl J Med.* 2006;355(9):896-908.
14. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for parkinson's disease with early motor complications. *N Engl J Med.* 2013;368(7):610-622.
15. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced parkinson disease: A randomized controlled trial. *JAMA.* 2009;301(1):63-73.
16. Odekerken VJ, van Laar T, Staal MJ, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced parkinson's disease (NSTAPS study): A randomised controlled trial. *Lancet Neurol.* 2013;12(1):37-44.
17. Goetz CG, Tilley BC, Shaftman SR, et al. Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov Disord.* 2008;23(15):2129-2170.

18. Reuben DB, Magasi S, McCreath HE, et al. Motor assessment using the NIH toolbox. *Neurology*. 2013;80(11 Suppl 3):S65-75.

19. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with parkinson's disease. *Qual Life Res*. 1995;4(3):241-248.

20. Appleby BS, Duggan PS, Regenberg A, Rabins PV. Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: A meta-analysis of ten years' experience. *Mov Disord*. 2007;22(12):1722-1728.

21. Janssen ML, Duits AA, Tourai AM, et al. Subthalamic nucleus high-frequency stimulation for advanced parkinson's disease: Motor and neuropsychological outcome after 10 years. *Stereotact Funct Neurosurg*. 2014;92(6):381-387.

22. Okun MS, Fernandez HH, Wu SS, et al. Cognition and mood in parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: The COMPARE trial. *Ann Neurol*. 2009;65(5):586-595.

23. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in parkinson's disease: A multicentre study with 4 years follow-up. *Brain*. 2005;128(Pt 10):2240-2249.

24. Okun MS, Gallo BV, Mandybur G, et al. Subthalamic deep brain stimulation with a constant-current device in parkinson's disease: An open-label randomised controlled trial. *Lancet Neurol*. 2012;11(2):140-149.

25. Guehl D, Dehail P, de Seze MP, et al. Evolution of postural stability after subthalamic nucleus stimulation in parkinson's disease: A combined clinical and posturometric study. *Exp Brain Res*. 2006;170(2):206-215.

26. Maurer C, Mergner T, Xie J, Faist M, Pollak P, Lucking CH. Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in parkinson's disease. *Brain*. 2003;126(Pt 5):1146-1163.

27. St George RJ, Carlson-Kuhta P, Burchiel KJ, Hogarth P, Frank N, Horak FB. The effects of subthalamic and pallidal deep brain stimulation on postural responses in patients with parkinson disease. *J Neurosurg*. 2012;116(6):1347-1356.

28. Katz M, San Luciano M, Carlson K, et al. The differential effects of DBS target on motor subtypes in parkinson's disease. *Ann Neurol*. 2015.

29. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for parkinson's disease. *N Engl J Med*. 2010;362(22):2077-2091.

30. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for parkinson disease: An expert consensus and review of key issues. *Arch Neurol*. 2011;68(2):165.