Thalamic Deep Brain Stimulation for Secondary Dystonia in Children and Young Adults

NCT03078816

March 3, 2017

Study Application (Version 1.11)

1.0 General Information

***Enter the full title of your study:**

Thalamic DBS for Secondary Dystonia

***Enter the study number or study alias**

DBSVop
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add Department(s)

2.1 List the departments associated with this study. The Principal Investigator's department should be Primary.:

Primary Dept?	Department Name
○	**UCSF** - *200044* - Neurosurgery
◉	**UCSF** - *140020* - M_Neurology

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

San Luciano Palenzuela, Marta M.D., MD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Bledsoe, Ian MD
Other Investigator
Demopoulos, Carly PhD
Other Investigator
Larson, Paul S, MD
Other Investigator
Ostrem, Jill M.D.

Other Investigator
Racine, Caroline
Other Investigator
Starr, Philip MD, PhD
Other Investigator
Volz, Monica M
Study Clinician
Wang, Sarah S
Other Investigator
Watson, Christa L
Other Investigator

B) Research Support Staff

Gittings, Melissa L
Study Coordinator
Viser, Aaron
Study Coordinator

3.3 *Please add a Study Contact:

Wang, Sarah S

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Initial Screening Questions

Updated June 2017

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here: Click on the orange question mark to the right for more detailed instructions.

Dystonia is a movement disorder seen in both children and adults that is characterized by "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both." Secondary dystonia has evolved to refer to dystonia resulting from damage to the nervous system or degenerative disease processes. While primary dystonia is generally thought to arise from genetic causes, secondary dystonias have a variety of causes including perinatal injuries (cerebral palsy), central nervous system infections, traumatic brain injuries, and many different metabolic, neurodegenerative, and mitochondrial conditions. Secondary dystonia is far more common in pediatric populations than primary dystonia, and far more recalcitrant to standard pharmacologic and surgical treatments including Deep Brain Stimulation. Given that most treatments for dystonia are developed for primary dystonia and then applied to secondary dystonia, it is not surprising that this effectiveness gap exists. Thus, there exists a

large unmet need to develop new therapeutics, treatment strategies, and outcome measures for pediatric secondary dystonia[2].

Deep Brain Stimulation (DBS) is one such therapeutic intervention that has potential to improve secondary dystonia. DBS is a surgical treatment for several different movement disorders that evolved from functional stereotactic neurosurgery techniques initially used to lesion specific deep brain structures[3]. While Essential Tremor and Idiopathic Parkinson's Disease have predictable and consistent response rates to DBS in carefully selected patients, response rates of dystonia have been much more inconsistent. One predictor of success has been the presence of DYT-1 mutation, the most common known genetic cause of primary dystonia [12]. Success rates in DYT-1 dystonia are consistently high with reductions in dystonia typically greater than 80%[13–15] . However, the results in secondary dystonia have been much more modest and inconsistent. A recent meta-analysis found that on average, dystonia symptoms as measured by common rating scales improve 23% following DBS for dystonic cerebral palsy (the most common cause of secondary dystonia), however there are frequent cases of non-responders[16]. Additionally, there have been very few examination, radiological or laboratory predictors of good response to DBS, except for genetic confirmation of DYT-1[17]. However, across both primary and secondary dystonia, younger age at the time of surgery (less than 21 years old) and shorter duration of symptoms (less than 15 years) have been shown to be the most likely predictive factors for a good postoperative outcome[17]. This has led many to suggest that DBS should be offered earlier in the course of intractable dystonia, prior to the development of permanent complications such as orthopedic contractures. Thus, we are setting an upper age limit of 25 to account for the concern that earlier implantation leads to improved outcomes. The lower age limit of 7 reflects the fact that the current humanitarian exemption for DBS for dystonia currently goes down to age 7. Thus, there exists a need to both improve patient selection as well as application of DBS for secondary dystonia in children. This study has been approved by the FDA under an investigational device exemption (IDE #G160233).

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

- (•) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (Click the Help link for definitions and guidance): (REQUIRED)

- (•) Biomedical research
- ( ) Social, behavioral, educational, and/or public policy research
- ( ) Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social /behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RADIATION EXPOSURE: Does your protocol involve any radiation exposure to patients/subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans): (REQUIRED)

- ( ) Yes (•) No

4.6 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities (Help Text updated 9/13):

- ( ) Minimal risk
- (•) Greater than minimal risk

4.7 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

- (•) Full Committee
- ( ) Expedited
- ( ) Exempt

4.11 * CLINICAL TRIAL: (REQUIRED) Is this a clinical trial? According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- **Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.**

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals. Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called ClinicalTrials.gov. The FDA requires registration for "applicable clinical trials," defined as follows:

- **For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.**
- **For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.**

For additional information on the ClinicalTrials.gov registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB.

(•) Yes ( ) No

Clinical Trial Registration

"NCT" number for this trial:

to be determined

If you don't yet have the NCT#, type 'Pending.'

4.12 * CLINICAL TRIAL PHASE (REQUIRED) Check the applicable phase(s) (Help Text updated 9/13):

- [x] Phase I
- [ ] Phase II
- [ ] Phase III
- [ ] Phase IV

4.13 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

(•) Yes ( ) No

4.14 SCIENTIFIC REVIEW: If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Services (CRS) Advisory Committee
- [x] CTSI Consultation Services
- [ ] Departmental scientific review
- [ ] Other:

4.15 * STEM CELLS: (REQUIRED) Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

- (•) No
- ( ) Yes, and requires CHR and GESCR review
- ( ) Yes, and requires GESCR review, but NOT CHR review

4.16 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

( ) Yes (•) No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

( ) Yes (•) No

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

( ) Yes (•) No

5.3 SPONSORS: Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)
No Sponsor has been added to this IRB Study						

If the funding is coming through UCSF and you don't know the A or P number, you can search the eProposal side for the contract or grant (this does NOT replace adding the sponsor by name above AND entering the A or P number):

Project Status	Proposal Number	Project Title	Principal Investigator
No Projects are Linked to this IRB Study			

Other Funding Sources and Unfunded Research - Gift, Program, or Internal Funding (check all that apply):

☐ Funded by gift (specify source below)

- [ ] Funded by UCSF or UC-wide program (specify source below)
- [ ] Specific departmental funding (specify source below)
- [ ] Unfunded (miscellaneous departmental funding)
- [ ] Unfunded student project

6.0 Sites, Programs, Resources, and External IRB Review

6.1 UCSF AND AFFILIATED SITES (check all that apply):

- [x] UCSF (including Laurel Heights and all the other sites outside the main hospitals)
- [ ] Parnassus
- [x] Mission Bay
- [ ] China Basin
- [x] Mount Zion
- [ ] Helen Diller Family Comprehensive Cancer Center
- [ ] Langley Porter Psychiatric Institute
- [ ] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Blood Centers of the Pacific (BCP)
- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno Community Medical Center
- [ ] Gallo
- [ ] Gladstone
- [ ] Jewish Home
- [ ] Institute on Aging (IOA)
- [ ] SF Dept of Public Health (DPH)

6.2 LOCATIONS: At what locations will study visits and activities occur:

Outpatient visits will take place in the Neurology Clinic at 1635 Divisadero St., Suite 520 or if necessary, at the Pediatric Brain Center at Mission Bay. Surgery will take place at the UCSF Benioff Children's Hospital in San Francisco. On some occasions when patients may not be able to afford to travel to UCSF for some study visits after the immediate post-operative phase, visits may be conducted by video conferencing (such as Zoom).

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

- ○ Yes
- ◉ No

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program

6.5 * CTSI CRS SERVICES: (REQUIRED) Will this study be carried out at one of the UCSF Clinical Research Services (CRS) units or utilize CRS services:

- ○ Yes
- ◉ No

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multicenter research trial? By multi-center trial, we mean a study where the protocol is developed by an industry sponsor, consortium, a disease-group, etc., who then selects sites across the nation or in different countries to participate in the trial. The local sites do not have any control over the design of the protocol.

○ Yes ◉ No

6.7 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project: Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor its affiliates are the coordinating center.

- ☐ Other UC Campus
- ☐ Other institution
- ☐ Other community-based site
- ☐ Foreign Country
- ☐ Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.10 * RELYING ON AN EXTERNAL IRB: Does this application include a request to rely on an a central IRB (other than the NCI CIRB) or an external IRB (UC, commercial, or institutional): (REQUIRED)

○ Yes ◉ No

7.0 Research Plan and Procedures

7.1 This new consolidated section requests information about:

- **Hypothesis**
- **Aims**
- **Study Design**
- **Background and Significance**
- **Preliminary Studies**
- **Procedures**
- **Statistical Methods**
- **References**

Later sections include:

- **Drugs and Devices**
- **Sample Size, Eligibility, and Subjects**
- **Recruitment and Consent**
- **Risks and Benefits**
- **Data and Safety Monitoring Plan**
- **Confidentiality, Privacy and Security**
- **Financial Considerations**
- **Qualifications of Personnel**
- **Other Approval and Registrations**

7.2 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove (Help Text updated 9/13):

Based on historical results of ventralis oral posterior (Vop) thalamotomy in secondary dystonia, Vop DBS will be safe and tolerable and will have improvements equal to or better than globus pallidal DBS in secondary dystonia in children and young adults.

7.3 AIMS: List the specific aims:

- Determine safety and tolerability of Vop stimulation in children and young adults with secondary dystonia
- Assess preliminary efficacy of Vop stimulation for reducing dystonia in children and young adults with secondary dystonia
- Assess preliminary effects of Vop stimulation on quality of life in children and young adults with secondary dystonia

7.4 DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.):

This is a single-center, open-label, phase I clinical trial to estimate the treatment effect size and to assess preliminary safety and tolerability of Deep Brain Stimulation (DBS) of the ventralis oralis posterior nucleus of the thalamus in children and young adults with secondary dystonia. Patients will be recruited from two movement disorders centers: UCSF Center for the Surgical Treatment of Movement Disorders at Mount Zion and the Pediatric Brain Center at Mission Bay. The study will be discussed with all patients and their families/caregivers who meet inclusion and exclusion criteria, and written informed consent will be obtained from those patients who wish to enroll in the study.

A small cohort of 15 subjects will be implanted in the first two years. All participants will undergo a battery of clinical dystonia rating scales, measures of mobility, and quality of life measures performed prospectively pre- and post-DBS. Patients will also undergo a neuropsychological battery before surgery and 12 months post-operatively. The neuropsychological battery will be customized for each patient and his /her expressive language abilities. The subjects will be examined every two months for one year following surgery and adjustments to the stimulation parameters will be made. The DBS stimulation parameters will be patient-specific and calibrated by the dystonia, mobility and quality of life rating scales. The changes in dystonia and quality of life rating scales at the end of 1 year of treatment will be compared to historical results from published DBS of globus pallidus interna for secondary dystonia and used to design a future larger, randomized clinical trial. All dystonia scales measuring motor involvement will be videotaped so the tapes can later be reviewed if necessary.

7.5 BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.g. why is this study needed) (space limit: one half page):

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

Dystonia is a movement disorder seen in both children and adults that is characterized by "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both." [1] Secondary dystonia is far more common in pediatric populations than primary dystonia, and far more recalcitrant to standard pharmacologic and surgical treatments including Deep Brain Stimulation (DBS). There exists a large unmet need to develop new therapeutics, treatment strategies, and outcome measures for pediatric secondary dystonia[2].
We are proposing to investigate the ventralis oral posterior nucleus (Vop) of the thalamus as a new target for DBS in secondary dystonia. Prior to the development of DBS, the main surgical treatment of dystonia was thalamotomy[3]. Although there were many different targets in the thalamus, often done in staged procedures, the most common and successful targeted nuclei was the Vop, which is traditionally thought to be the pallidal receiving area[4]. Previous lesioning of Vop produced improvements in dystonia but intolerable side effects, especially when implanted bilaterally[4–6]. However, given that secondary dystonia patients were often reported to have superior results to primary dystonia[5,7], it is reasonable to believe that if the side effects can be modulated, that targeting of the Vop nucleus with DBS could be a viable

alternative to GPi. Given that DBS is a treatment that is inherently adjustable, it is conceivable that settings on the DBS could be adjusted to allow for clinical benefit with minimal side effects. Indeed, there have been several scattered successful case reports attesting to this possibility[8,9].

7.6 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

none

7.7 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

(•) Yes ( ) No

7.8 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- [x] Interviews, questionnaires, surveys
- [x] Educational or cognitive tests
- [ ] Focus groups
- [x] Observation
- [x] Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- [ ] Administration of contrast agent
- [x] Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- [ ] Biopsy conducted solely for research purposes
- [ ] Use of placebo
- [ ] Sham surgical procedure
- [ ] Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- [ ] Fitness tests or other exertion activities
- [ ] Use of mobile health apps or other apps
- [ ] Social media-based research activities
- [ ] None of the above

Please navigate back to section 4.0 Initial Screening Questions to change your answer to 4.4 about procedures involving radiation to 'Yes.' This will ensure that the Radiation Safety Committee receives a copy of your application when you first submit it to the IRB. Contact the Radiation Safety Commitee if you are not sure if radiation is involved.

7.9 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring
- additional biopsies to collect tissue for research
- extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

Screening Visit (within 120 days of surgical date)
Clinical visit to determine initial eligibility for DBS therapy. This will include a clinical movement disorders neurology evaluation and/or a clinical surgical evalueation, including review of MRI brain.

Informed Consent
Written informed consent (and assent if indicated) will be obtained from all patients before enrollment in the study. All potential subjects and/or legal guardians will be properly informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected and the option of undergoing DBS surgery outside of the study under an HDE. Key parts of the consent will be read out loud by a study investigator while the subject and/or guardian reads along and is asked if they understand the consent form. The Investigator will retain the original copy of the Informed Consent Form signed by the patient, and a duplicate will be provided to the patient.

Baseline Assessment
A baseline assessment will be completed prior to the DBS system implantation in all patients. Baseline evaluation will consist of reviewing/obtaining the following:

- Inclusion/Exclusion criteria
- Complete demographic information
- Complete medical history and physical examination
- Medication history (last 90 days)
- Screening MRI of the brain
- Clinical rating scales of motor function (videotaped):
    - Burke-Fahn Marsden Dystonia Rating Scale (BFMDRS)
    - Barry Albright Dystonia Scale (BADS)
    - Modified Ashworth Scale (MAS) (when possible)
    - Gross Motor Function Measure (GMFM) (when possible)
    - Modified UPDRS II
- Caregiver administed rating scales
    - PEDI-CAT (Pediatric Evaluation of Disability Inventory Computer Admistrated Test)
    - PedsQL (Pediatric Quality of Life Inventory)
- Neuropsychological Battery: tailored to subject's expressive language ability, but likely to include tests of:
    - non-verbal intellectual abilities (Matrix Reasoning, Picture Concepts, and Picture Completion [subtests of the Wechsler Intelligence Scale for Children, the Wechsler Abbreviated Scale of Intelligence, and the Wechsler Pre-school and Primary Scale of Intelligence)
    - verbal intellectual abilities (Vocabulary, Similarities, Information, and Picture Vocabulary [subtests of the Wechsler Intelligence Scale for Children])
        - memory (Memory for Faces, Dot Locations, and Digit Span [subtests of the Children’s Memory Scale])
        - mood/behavior (BASC-3: Self Report of Personality)
    - Formal measurements of speech and articulation abilities
    - Assessments for depression
- Blood or urine pregnancy test to be done with standard pre-operative labs, up to 30 days before surgery.

This baseline evaluation for a non-study patient treated under the HDE would include all of the above except for the MAS, GMFM, Pedi-CAT, PedsQL, and Neuropsychological Testing.

DBS System Implantation

If blood or urine pregnancy test is not done as part of standard clinical preoperative labs, a test will be done on the day of surgery.

Implantation of the DBS system will be performed according to standard surgical procedures under general anesthesia. Patients will be given an intravenous dose of antibiotics perioperatively and for no less than 48 hours after surgery. Patients will be sent home with 10 days of antibiotics.

The DBS system implant procedure would be the same as for patients consented under the Humanitarian Device Exemption for clinical care of primary dystonia and typical off label use of DBS for secondary dystonia (IRB# 10-01285), except the electrodes will be placed in the thalamus instead of the globus pallidus. The infection protocol (IV antibiotics + 10 days of antibiotics post-op) is also different from usual clinical care.

Post-operative visit 1 and initiation of device use (12 days after surgery +/- 3 days)

- Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
- Record changes to concomitant medications
- Perform abbreviated physical examination
- Perform and record vital signs
- Initial activation of DBS device
- Videotaped dystonia rating scales (BADS, BFMDRS) (prior to and following activation of DBS)

Once the patient's system is programmed, the patient will receive a hand-held device to identify if the system is on or off and to slightly modify their settings if their symptoms necessitate. Patients will be seen every two months for programming adjustments, but may be seen at any time during the study to optimize programming.

All of the above is standard of care for post-operative visit 1 except the videotaping of dystonia rating scales.

Post-operative (months 2-11): Visits every 8 weeks +/- 14 days after initial programming appointment for adjustments to DBS settings

- Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
- Record changes to concomitant medications.
- Perform abbreviated physical examination.
- Perform and record vital signs.
- Dystonia rating scales (BFMDRS, BADS)
- Optimize stimulator settings for best clinical benefit
- At the Month 6 visit, we will administer the PedsQL, UPDRS II, and the Modified Ashworth Scale (when possible)

All of the above is consistent with standard of care, except the PedsQL and Modified Ashworth Scale at the 6 month visit

Post-operative month 12 visit: 52 weeks +/- 14 days from surgical date

- Record any Adverse Experiences and/or Review subject diary for adverse experiences and exclusionary medication use.
- Record changes to concomitant medications.
- Perform complete physical examination.
- Perform and record vital signs.
- Clinical rating scales of motor function (videotaped):
    - Burke-Fahn Marsden Dystonia Rating Scale (BFMDRS)
    - Barry Albright Dystonia Scale (BADS)
    - Modified Ashworth Scale (MAS) (when possible)
    - Gross Motor Function Measure (GMFM) (when possible)
    - Modified UPDRS II
- Caregiver administed rating scales
    - PEDI-CAT (Pediatric Evaluation of Disability Inventory Computer Admistrated Test)
    - PedsQL (Pediatric Quality of Life Inventory)
- Neuropsychological Battery: tailored to subject's expressive language ability, but likely to include tests of:
    - non-verbal intellectual abilities (Matrix Reasoning, Picture Concepts, and Picture Completion [subtests of the Wechsler Intelligence Scale for Children, the Wechsler Abbreviated Scale of Intelligence, and the Wechsler Pre-school and Primary Scale of Intelligence)
    - verbal intellectual abilities (Vocabulary, Similarities, Information, and Picture Vocabulary [subtests of the Wechsler Intelligence Scale for Children])
        - memory (Memory for Faces, Dot Locations, and Digit Span [subtests of the Children's Memory Scale])

- mood/behavior (BASC-3: Self Report of Personality)

This baseline evaluation for a non-study patient treated under the HDE would include all of the above except for the adverse event diary, MAS, GMFM, Pedi-CAT, PedsQL, and Neuropsychological Testing.

All of the above is consistent with standard of care except for adverse event diary, Modified Ashworth Scale, and PedsQL.

No additional post-op visits are included in this study compared to what is recommended for routine clinical care under the HDE. Follow-up evaluations with formal neurological examination and videotaping are important for the programming of the DBS devices. If the patient agrees to participate in research, the only additional step will be additional mobility and quality of life scales, neuropsychological testing and that the results of their formal neurological examinations (clinical rating scores and neuropsychological testing), will be pooled with those of other patients in this study, statistically analyzed, and the results will be published.

7.10 STANDARD CLINICAL PRACTICE: To what extent, if any, do the planned research procedures differ from the care that people would otherwise receive at this institution or the study site if not being done locally:

DBS is occasionally implanted in the globus pallidus interna (GPi) in patients with secondary dystonia as an off-label use of the device; the frequency of DBS use in secondary dystonia varies between institutions. In recent years, at our institution (UCSF), we have not frequently offered DBS for secondary dystonia given that stimulation in the globus pallidus has not led to a substantial enough benefit to warrant the risks and costs associated with the procedure. Given that historically thalamotomy for secondary dystonia has produced better results, we believe that thalamic DBS has a greater potential to produce substantial benefits than pallidal DBS. Thus, for this study, the electrodes will be placed in the thalamus, not in the globus pallidus. Otherwise, the only differences from standard of care for DBS for dystonia will be neuropsychological testing at pre-operative visit and month 12 visit, as well as obtaining additional rating scales (PEDI-CAT, GMFM, PedsQL). The number of clinical visits remains the same.

7.11 INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used for this study:

Clinical rating scales of motor function:

- Validated
  - Burke-Fahn Marsden Dystonia Rating Scale (BFMDRS)
  - Barry Albright Dystonia Scale (BADS)
  - Modified Ashworth Scale (MAS)
  - Gross Motor Function Measure (GMFM)
- Unvalidated
  - Modified UPDRS II for Secondary Dystonia (experimental)

Caregiver administered rating scales:

- Validated
  - PEDI-CAT (Pediatric Evaluation of Disability Inventory Computer Administrated Test)
  - PedsQL (Pediatric Quality of Life Inventory)

Neuropsychological testing: Baseline and one year follow up neuropsychological evaluation will be performed using standardized tests when possible. The testing will be customized to each child or young adult according his or her age and ability to communicate and access the materials physically. Attempts will be made to include the following test battery or comparable tests: (1) non-verbal intellectual abilities (Matrix Reasoning, Picture Concepts, and Picture Completion [subtests of the Wechsler Intelligence Scale for Children, the Wechsler Abbreviated Scale of Intelligence, and the Wechsler Pre-school and Primary Scale of Intelligence)(2) verbal intellectual abilities (Vocabulary, Similarities, Information, and Picture Vocabulary [subtests of the Wechsler Intelligence Scale for Children]) (3) memory (Memory for Faces, Dot Locations, and Digit Span [subtests of the Children's Memory Scale]) and (4) mood/behavior (BASC-3: Self Report of Personality)

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

7.12 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.): (REQUIRED)

○ Yes ◉ No

7.25 STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed:

All of the dystonia clinical rating scale measures will be measured pre-operatively and post-operatively after 1 year of continuous stimulation and the measures at the two time points will be compared using the Wilcoxon signed-rank test for matched pairs.

7.26 REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with):

1. Mink JW. Special concerns in defining, studying, and treating dystonia in children. *Mov Disord*. 2013;28:921-925. doi:10.1002/mds.25548.
2. Sironi VA. Origin and evolution of deep brain stimulation. *Front Integr Neurosci*. 2011;5:42. doi:10.3389/fnint.2011.00042.
3. Franzini A, Cordella R, Messina G, et al. Targeting the brain: Considerations in 332 consecutive patients treated by deep brain stimulation (DBS) for severe neurological diseases. *Neurol Sci*. 2012;33(6):1285-1303. doi:10.1007/s10072-012-0937-9.
4. Panov F, Gologorsky Y, Connors G, Tagliati M, Miravite J, Alterman RL. Deep brain stimulation in DYT1 dystonia: A 10-year experience. *Neurosurgery*. 2013;73:86-93. doi: 10.1227/01.neu.0000429841.84083.c8.
5. Cif L, Vasques X, Gonzalez V, et al. Long-term follow-up of DYT1 dystonia patients treated by deep brain stimulation: An open-label study. *Mov Disord*. 2010;25:289-299. doi:10.1002/mds.22802.
6. Air EL, Ostrem JL, Sanger TD, Starr PA. Deep brain stimulation in children: experience and technical pearls. *J Neurosurg Pediatr*. 2011;8:566-574. doi:10.3171/2011.8.PEDS11153.
7. Koy A, Hellmich M, Pauls KAM, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: A meta-analysis. *Mov Disord*. 2013;28:647-654. doi:10.1002/mds.25339.
8. Vidailhet M, Jutras M-F, Grabli D, Roze E. Deep brain stimulation for dystonia. *J Neurol Neurosurg Psychiatry*. 2013;84:1029-1042. doi:10.1136/jnnp-2011-301714.
9. Hyam J a., Owen SLF, Kringelbach ML, et al. Contrasting connectivity of the ventralis intermedius and ventralis oralis posterior nuclei of the motor thalamus demonstrated by probabilistic tractography. *Neurosurgery*. 2012;70(1):162-169. doi: 10.1227/NEU.0b013e3182262c9a.
10. Andrew J, Fowler CJ, Harrison MJ. Stereotaxic thalamotomy in 55 cases of dystonia. *Brain*. 1983;106 (Pt 4:981-1000.
11. Burchiel KJ. Thalamotomy for movement disorders. *Neurosurg Clin N Am*. 1995;6:55-71.
12. Cardoso F, Jankovic J, Grossman RG, Hamilton WJ, Kelly PJ, Tasker RR. Outcome after stereotactic thalamotomy for dystonia and hemiballismus. *Neurosurgery*. 1995;36:501-508. doi:10.1227/00006123-199503000-00009.
13. S. H, N. T, T. T. Safety and efficacy of stereotactic ventrooral-thalamotomy for musician's dystonia. *Mov Disord*. 2014;29:S504.
14. Kim JP, Chang WS, Chang JW. Treatment of secondary dystonia with a combined stereotactic procedure: Long-term surgical outcomes. *Acta Neurochir (Wien)*. 2011;153:2319-2327. doi:10.1007/s00701-011-1147-6.
15. Vidailhet M, Yelnik J, Lagrange C, et al. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. *Lancet Neurol*. 2009;8(8):709-717. doi:10.1016/S1474-4422(09)70151-6.
16. Binder DK, Rau GM, Starr P a. Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. *Neurosurgery*. 2005;56(4):722-728. doi:10.1227/01.NEU.0000156473.57196.7E.
17. Sillay K, Larson P, Starr P. DEEP BRAIN STIMULATOR HARDWARE-RELATED INFECTIONS: INCIDENCE AND MANAGEMENT IN A LARGE SERIES. *Neurosurgery*. 2008;62(2):360-367. doi:10.1227/01.NEU.0000297020.60125.FC.

8.0 Drugs and Devices

8.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

○ Yes ◉ No

Note: This question is frequently answered incorrectly. If any drugs or biologics, approved or unapproved, are being administered under this protocol, you should check 'Yes' unless you are *absolutely* sure that NONE of the drugs are part of the research protocol. Tip: Ask the PI or the sponsor if you are not sure how to answer this question.

8.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

◉ Yes ○ No

8.4 * NSR: Are you requesting a Non-Significant Risk (NSR) determination for an investigational device: (REQUIRED) Note: an NSR determination is different from an Investigational Device Exemption (IDE). Check the Help link for more guidance on what types of devices can qualify for an NSR determination.

○ Yes ◉ No

8.5 LIST THE DEVICES: List the medical devices or in vitro diagnostics to be studied or used. In the device details screen you will be asked questions such as:

- **Whether the device is FDA approved or investigational**
- **Medicare device category**
- **If the device will be provided at no cost**
- **If an IDE is necessary, the IDE number, and who holds the IDE**
- **Risk category of the device**
- **FDA status of the device**

Please see the UCSF IRB website for more details about the use of devices in research, including the Investigator Checklist for Significant Risk, Non-Significant Risk, and/or IDE Exempt Device Studies
Verification of IDE numbers: If the sponsor's protocol does not list the IDE number, you must submit documentation from the sponsor or FDA identifying the IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet.
If you have any correspondence from the FDA or sponsor regarding this device, please attach it to the application.

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	Activa PC Primary Cell Neurostimulator	Yes	Yes	G160233

Manufacturer/Supplier of Device	Medtronic
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
Will Devices be supplied at no Cost	No
Is this a HUD (HDE)	No

HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	Yes
IDE Number	G160233
Who holds the IDE	PI holds the IDE
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk

⊟	Activa SC Single Cell Neurostimulator	Yes	Yes	G160233

Manufacturer/Supplier of Device	Medtronic
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	Yes
IDE Number	G160233
Who holds the IDE	PI holds the IDE
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

⊟	Neurostimulator	Yes	Yes	G160233

Manufacturer/Supplier of Device	Medtronic
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
Will Devices be supplied at no Cost	No
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	Yes
IDE Number	G160233
Who holds the IDE	PI holds the IDE
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk

⊟	DBS Lead	Yes	Yes	G160233

Manufacturer/Supplier of Device	Medtronic
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
Will Devices be supplied at no Cost	No
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	Yes
IDE Number	G160233
Who holds the IDE	PI holds the IDE
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk

⊟	Activa SC Single Cell Neurostimulator	Yes	Yes	G160233

Manufacturer/Supplier of Device	Medtronic
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
Will Devices be supplied at no Cost	No
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	Yes
IDE Number	G160233
Who holds the IDE	N/A
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk

⊟	Medtronic DBS extension	Yes	Yes	G160233

Manufacturer/Supplier of Device	Medtronic
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
Will Devices be supplied at no Cost	No
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes

	Is this a new device or a new use of an already approved device	Yes		
	Is an IDE necessary	Yes		
	IDE Number	G160233		
	Who holds the IDE	PI holds the IDE		
	IDE Details			
	In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk		
⊟	DBS Extension	Yes	Yes	G160233
	Manufacturer/Supplier of Device	Medtronic		
	Medicare Category	☐ A ☐ B		
	Where will the Devices Be Stored			
	Will Devices be supplied at no Cost	No		
	Is this a HUD (HDE)	No		
	HDE Number			
	Is the Device FDA Approved	Yes		
	Is this a new device or a new use of an already approved device	Yes		
	Is an IDE necessary	Yes		
	IDE Number	G160233		
	Who holds the IDE	PI holds the IDE		
	IDE Details			
	In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk		
⊟	Patient Programmer	Yes	Yes	G160233
	Manufacturer/Supplier of Device	Medtronic		
	Medicare Category	☐ A ☐ B		
	Where will the Devices Be Stored			
	Will Devices be supplied at no Cost	No		
	Is this a HUD (HDE)	No		
	HDE Number			
	Is the Device FDA Approved	Yes		
	Is this a new device or a new use of an already approved device	Yes		
	Is an IDE necessary	Yes		
	IDE Number	G160233		
	Who holds the IDE	PI holds the IDE		
	IDE Details			
	In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk		
⊟	Test Stimulator	Yes	Yes	G160233

Manufacturer/Supplier of Device	Medtronic			
Medicare Category	☐ A ☐ B			
Where will the Devices Be Stored				
Will Devices be supplied at no Cost	No			
Is this a HUD (HDE)	No			
HDE Number				
Is the Device FDA Approved	Yes			
Is this a new device or a new use of an already approved device	Yes			
Is an IDE necessary	Yes			
IDE Number	G160233			
Who holds the IDE	PI holds the IDE			
IDE Details				
In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk			
⊟	N'Vision Clinician Programmer	Yes	Yes	G160233
Manufacturer/Supplier of Device	Medtronic			
Medicare Category	☐ A ☐ B			
Where will the Devices Be Stored				
Will Devices be supplied at no Cost	No			
Is this a HUD (HDE)	No			
HDE Number				
Is the Device FDA Approved	Yes			
Is this a new device or a new use of an already approved device	Yes			
Is an IDE necessary	Yes			
IDE Number	G160233			
Who holds the IDE	PI holds the IDE			
IDE Details				
In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk			
⊟	N'Vision Software Application Card	Yes	Yes	G160233
Manufacturer/Supplier of Device	Medtronic			
Medicare Category	☐ A ☐ B			
Where will the Devices Be Stored				
Will Devices be supplied at no Cost	No			
Is this a HUD (HDE)	No			
HDE Number				
Is the Device FDA Approved	Yes			
Is this a new device or a new use of an already approved device	Yes			

Is an IDE necessary	Yes
IDE Number	G160233
Who holds the IDE	PI holds the IDE
IDE Details	
In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk

8.6 * Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (REQUIRED)

- ○ Yes
- ◉ No

9.0 Sample Size and Eligibility Criteria

9.1 ENROLLMENT TARGET: How many people will you enroll:

17

If there are multiple participant groups, indicate how many people will be in each group:

9.3 SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites:

This is a phase I pilot study of 15 participants to determine safety and tolerability as well as estimate effect size to inform planning of future larger trials that will test effectiveness. There is not sufficient data on the efficacy outcome measures to calculate sample size using statistical methods, thus the number of subjects was estimated based on a similar prospective study of DBS of globus pallidus (GPi) in adults with secondary dystonia in which a significant improvement was found using 13 subjects. We will screen up to 17 patients to achieve a total of 15 implanted.

9.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- ☐ 0-6 years
- ☑ 7-12 years
- ☑ 13-17 years
- ☑ 18-64 years
- ☐ 65+

9.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- ☑ Inpatients
- ☑ Outpatients
- ☑ Family members or caregivers
- ☐ Providers
- ☐ People who have a condition but who are not being seen as patients
- ☐ Healthy volunteers
- ☐ Students

- [ ] Staff of UCSF or affiliated institutions
- [ ] None of the above

9.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

- [x] Children / Minors
- [x] Subjects unable to consent for themselves
- [ ] Subjects unable to consent for themselves (emergency setting)
- [x] Subjects with diminished capacity to consent
- [x] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners
- [ ] Economically or educationally disadvantaged persons
- [ ] None of the above

If not already addressed in the Background and Significance questions in the Research Plan section or elsewhere, explain why it is appropriate to include the types of subjects checked above in this particular study:

The intervention is aimed at children and young adults because data from Deep Brain Stimulation (DBS) in other sites in the brain (globus pallidus) suggests that the earlier in the disease course DBS if performed the better the outcome. DBS of globus pallidus has been shown to be safe and effective in children as young as 7 years of age.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Here are some examples:

- evaluating capacity to consent for individuals who may be decisionally impaired (specify how)
- calibrating payment amounts to be non-coercive for the financially disadvantaged
- conducting more in-depth evaluations of subjects' understanding of the study and the voluntary nature of participation
- involving advocates in the consent process

More information and other safeguards are described here: **Vulnerable Subject Populations** and **Recruiting Staff and Students**.

Children and adolescents ages 7-17 will be asked to give verbal assent to the procedure. Subjects age 18 and over who are unable to give informed consent will have a surrogate give informed consent on their behalf.

9.7 INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.):

1. Male or female between 7-25 years of age at Visit 2 (day of surgery).
2. Documentation of a secondary dystonia diagnosis as determined by a fellowship trained movement disorders specialist, including either abnormality on brain MRI or history of hypoxic-ischemic brain injury preceding onset of dystonia symptoms.
3. Symptoms present for at least 6 months.

4. Written informed consent and assent (when applicable) obtained from participant or participant's legal representative and ability for participant to comply with the requirements of the study.
5. Dystonia symptoms that are sufficiently severe, in spite of best medical therapy, to warrant surgical implantation of deep brain stimulators in the clinical opinion of the treating physician
6. Minimum score of Burke-Fahn-Marsden Rating Scale and/or Barry-Albright Dystonia Rating Scale of 6.
7. Stable doses of anti-dystonia medications (such as levodopa, baclofen, or diazepam) for at least 30 days prior to baseline assessment
8. If participant receives botulinum toxin injections, patient should be on a stable injection regimen (as defined as no changes in past 4 months)
9. Intact thalamic anatomy as determined by standard clinical MRI in the past 2 years.
10. Patient has been clinically determined to be a good candidate for deep brain stimulation.
11. A caregiver willing to administer rating scales related to the study

9.8 EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study):

- Pregnancy or breast feeding
- Major comorbidity increasing the risk of surgery (severe hypertension, severe diabetes, or need for chronic anticoagulation other than aspirin)
- Inability to comply with study protocols or follow-up visits
- Uncontrolled epilepsy (more than 1 seizure in the past 6 months)
- Has an active infection
- Requires diathermy, electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) to treat a chronic condition
- Has an active implanted neurostimulator, cardiac pacemaker, drug pumps, defibrillators, or metallic implant in head.
- Dystonia caused by known genetic mutation in any DYT genes
- Subjects with secondary dystonias caused by tardive dyskinesia associated with psychotropic medications or an ongoing inflammatory or infectious process.
- Subjects with cognitive impairment or dementia as defined by an estimated IQ of less than 70 on nonverbal IQ measures.
- Subjects with uncontrolled depression as diagnosed by board certified psychiatrist
- Subjects with uncontrolled co-existing medical conditions: e.g., uncontrolled systemic hypertension with values above 170/100; active heart disease needing immediate intervention; active respiratory disease needing immediate intervention; uncorrected coagulation abnormalities;
- Contraindication to undergo a brain MRI
- Subjects who are immunocompromised, are on anticoagulation therapy that would preclude their ability to undergo the implant procedure, and are allergic or have shown hypersensitivity to any materials of the neurostimulation system which come into contact in the body

9.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on patient care units at UCSF medical facilities: (REQUIRED)

(•) Yes ( ) No

Attach a letter of acknowledgement for the study from the involved patient care manager. If you don't know who the patient care manager is, click here to send an email to the nursing group.

10.0 Inclusion of Minors in Research

10.1 REGULATORY CATEGORIES OF RESEARCH: Select all the regulatory categories that apply:

- [ ] No greater than minimal risk (45 CFR 46.404, 21 CFR 50.51)
- [x] Greater than minimal risk but presenting prospect of direct benefit (45 CFR 46.405, 21 CFR 50.52)
- [ ] Greater than minimal risk (though only a minor increase over minimal risk) and no prospect of direct benefit but likely to yield generalizable knowledge about the subjects disorder or condition (45 CFR 46.406, 21 CFR 50.53)
- [ ] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407, 21 CFR 50.54)

Explain why the research in this study falls under the above category or categories:

The study involves brain surgery that carries significant risk, but there is a good chance of substantial (>25%) reduction in dystonia symptoms with the intervention in the study.

10.2 MINORS CONSENTING: Will this study enroll minors who can legally consent for themselves (as in the case of emancipated minors or minors being treated for pregnancy or drug use without their parents knowing). This is different from agreeing to be in the study even when their parents are the ones providing 'official' consent, which we refer to as 'providing assent':

Note: This is very rare and the answer is usually 'No.'

- ( ) Yes
- (•) No

10.3 PARENTAL PERMISSION VS. WAIVER: Please review the guidance to see under what circumstances the IRB can waive parental permission.

- [x] Parental permission will be obtained
- [ ] Waiver of parental permission is requested: The waiver meets the provisions for a waiver of consent (i. e., the research poses minimal risk, it could not practicably be carried out without the waiver of parental permission, AND the waiver will not adversely affect the rights and welfare of the minor participants (45 CFR 46.116(d))
- [ ] Waiver of parental permission is requested: Parental permission is not a reasonable requirement to protect the minor (e.g. neglected or abused children) or parental knowledge of the study may endanger the health or welfare of the minor (45 CRF 46.408(c))

Provide details on the other protections that will be in place:

10.4 ASSENT OF MINORS OR WAIVER: Please review the guidance to see under what circumstances the IRB can waive assent.

- [x] Assent of children developmentally and psychologically able to provide assent will be obtained
- [x] Waiver of assent is requested: The capability of some or all of the children is so limited that they cannot reasonably be consulted
- [ ] Waiver of assent is requested: The research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research
- [ ] Waiver of assent is requested: The activities involving the minor are limited to chart review or the something equally innocuous
- [ ] Waiver of assent is requested: It is not culturally appropriate to involve the minor in the decision to participate (e.g. some foreign research)

Provide a brief justification for the waiver:

The disease processes that cause secondary dystonia can also impair children's ability to speak and provide assent, and thus we are requesting this waiver only for patients who are impaired.

10.5 DOCUMENTATION OF PERMISSION AND ASSENT: (select all that will be used):

- [x] Permission form addressed to the parents
- [x] Simplified assent form addressed to the child, 7-12 years old (parents get separate form)
- [ ] Assent form addressed to the child, 13 years and older (for subjects and parents)
- [x] Assent form addressed to the child, 13 years and older (parents get separate form)

Check one:

- (•) One parent's signature will be obtained
- ( ) Two parents' signatures will be obtained

If this study is approvable under regulatory category .405 and you plan to get permission from only one parent, explain why you think one parent's permission is sufficient:

10.6 WARDS OF THE STATE: Might this study enroll wards of the state:

( ) Yes (•) No

11.0 Recruitment and Consent

11.1 * RECRUITMENT METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- [x] Medical records review
- [ ] Recruitment registry
- [ ] Re-contact of participants from the investigators' previous studies
- [ ] Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- [ ] Referrals from the community / word of mouth
- [ ] Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- [ ] Online recruiting tool such as TrialSpark
- [ ] CTSI Recruitment Services unit
- [ ] Other method (describe below)

11.2 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

- [x] Investigators' own patients or patients seen within the same practice
- [ ] Patients not under the care of the investigators

How and by whom will records be accessed and searched (check all that apply):

- [x] Self-search in APeX or other medical records source
- [ ] Self-search using UCSF's Research Cohort Selection Tool
- [ ] CTSI Consultation Service Recruitment Services
- [ ] UCSF Academic Research Services (ARS)
- [ ] University of California Research Exchange (UC ReX)
- [ ] Other method (describe below)

11.3 DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined:

Eligibility will be determined by the Investigator. After the Investigator determines that the patient and caregivers understand the risks and benefits, comprehend the consent, and have received satisfactory answers to all questions and signed the consent, the Investigator will determine eligibility based upon a complete history and physical, evaluation of screening assessment tools, and determination as to whether the patient meets all of the inclusion criteria and none of the exclusion criteria.

11.4 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [x] Investigators/study team
- [ ] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [ ] Potential participant
- [ ] Other (explain below)

11.5 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [x] In person
- [ ] Phone
- [ ] Letter / email
- [ ] Website or app
- [ ] Other (explain below)

11.6 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

Patients referred to the UCSF movement disorders surgery clinics for surgical treatment of dystonia will be offered participation in this study, by Dr. Viehoever, or Dr. Starr, if they are appropriate candidates for surgical treatment of dystonia.

11.7 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [x] Sign a consent form at the end of the consent discussion (signed consent)
- [ ] Provide online 'eConsent' using DocuSign or another E-Signature system
- [ ] Click through a link in a survey or email after reading about the study and then complete the study online (electronic consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent)
- [ ] Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent)
- [x] Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)
- [ ] Not be able to provide consent (emergency waiver of consent - allowed for minimal risk research or greater than minimal risk research with an approved community consultation plan)
- [ ] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

11.8 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**
- **For studies using online recruitment and consent or consent via mail, provide details here.**

Consent will be obtained by Dr. Amy Viehoever, Dr. Philip Starr, study nurse or coordinator certified to obtain consent in the surgical movement disorders clinic at UCSF. Patients who are eligible for this research study may be offered the choice of having DBS surgery under this research protocol or continue with standard medical treatment. The consent form will be reviewed and signed following a detailed verbal discussion about the risks and benefits of the procedure. The assent form will be reviewed with the child and signed following a detailed discussion. The discussion will occur after review of history and physical exam shows the patient to be an appropriate candidate for DBS. Patients and caregivers will have an open-ended amount of time to review the consent form and sign it.

* It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: **(REQUIRED)**

Either the Principal Investigator, Dr. Amy Viehoever, the Study Nurse, Monica Volz, or the Study Coordinator, Kristen Dodenhoff, will obtain the consent forms.

Dr. Viehoever is an Assistant Professor in the Divisions of Child Neurology and Surgical Movement Disorders at UCSF. She sees patients at the UCSF Pediatric Brain Center at Benioff Children's Hospital and Mt. Zion Campus. Dr. Viehoever's research focuses on improving the use of Deep Brain Stimulation (DBS) for pediatric primary and secondary dystonia, including Cerebral Palsy. She also uses advanced MRI and optical imaging to improve our understanding of how DBS improves brain function in both adult and pediatric patients. She also is a member of the Wolfram Study Group, a multidisciplinary collaboration to study the natural history of Wolfram Syndrome. She is an expert in optical imaging and using functional imaging to study neurologic disorders.

Monica Volz, MS, RN, is a clinical nurse specialist with 10 years of experience managing clinical trials and movement disorders patients treated with deep brain stimulation.

Kristen Dodenhoff is a clinical research coordinator with experience coordinating and obtaining consent for multiple studies being conducted within the Movement Disorders and Neuromodulation Center.

11.9 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

- [x] The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation
- [ ] Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or through a mobile health app)
- [ ] Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

Investigator(s) will meet with the subject to review the consent form and answer all questions. If the Investigator determines that the subject and parent or legal guardian does not fully understand or is hesitant, he/she will not be enrolled.

11.11 * NON-ENGLISH CONSENT METHOD: Indicate which method(s) you will use to consent non-English speaking subjects: (REQUIRED)

- [ ] Preferred Method—Consent form and other study documents will be available in the subject's primary language Personnel able to discuss participation in the patient's language will be present for the consent process.
- [x] Short-Form—A qualified interpreter will translate the consent form verbally, and subjects will be given the Experimental Subject's Bill of Rights in their primary language, following instructions in Those Who do not Read, Speak or Understand English for required witnessing and signatures

* Explain how you will maintain the ability to communicate with non-English speakers throughout their participation in the study: **(REQUIRED)**

If a member of the study staff speaks the primary language, we will communicate with the participant directly throughout their participation. If there is no member of the study staff who speaks the participant's primary language, a qualified interpreter will be hired for all visits. Qualified interpreters will be present for the informed consent process for all patients.

11.13 TIME: What is the estimated time commitment for participants (per visit and in total):

Participation in the study will take a total of about 48 hours for the surgery and the related ICU stay (patient will be discharged from the ICU) , and 24 hours over a period of 12 months for outpatient study visits.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

11.14 ALTERNATIVES: Is there a standard of care (SOC) or usual care that would be offered to prospective participants at UCSF (or the study site) if they did not participate in this research study:

- (•) Yes
- ( ) No

Describe the care that patients would ordinarily receive at the medical center if they did not participate in this study (provide details, assuming that some of the IRB members are not specialists in this field):

Other treatments for dystonia include medications and injections into the muscles of botulinum toxin. All patients being offered DBS surgery have already tried the appropriate treatments and have received inadequate benefit. Thus, the only alternative to DBS surgery is to continue to derive as much benefit as possible from medications and botulinum toxin injections.

11.15 OFF-STUDY TREATMENT: Is the study drug or treatment available off-study:

- ( ) Yes
- (•) No
- ( ) Not applicable

12.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when medical records may be reviewed to determine eligibility for recruitment.

12.1 * PRACTICABILITY OF OBTAINING CONSENT PRIOR TO ACCESS: Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified: (REQUIRED)

- (•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

12.2 * RISK TO PRIVACY: A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

12.3 * RIGHTS/WELFARE: Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

12.4 * IDENTIFIERS: Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [x] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

12.5 * HEALTH INFORMATION: Describe any health information that will be collected prior to obtaining informed consent:

Patients recruited for this study will be clinical patients referred to the care of Dr. Viehoever for DBS evaluation. Health information that is collected prior the obtaining informed consent will be information

necessary for the standard clinical care of patients including the identifiers indicated above. Any research-related information will be collected after obtaining informed consent.

Note: HIPAA requires that you collect the minimum necessary.

12.6 * DATA RETENTION/DESTRUCTION PLAN: Describe your plan to destroy any identifiable data collected to determine eligibility for recruitment. This should be done at the earliest opportunity. If you plan to retain identifiable recruitment data, provide the justification for doing so:

As long as the study is in progress patient names and medical records numbers will be retained in th e research database. At the time the study is completed or a patient is deamed ineligible for the study, UCSF patient names, medical records numbers, and health information will be deleted from the research database.

13.0 Surrogate Consent

13.1 PSYCHIATRIC SCREEN: Are any subjects inpatients on a psychiatric ward or mental health facility, or on psychiatric hold:

(•) No

If Yes, use of surrogate consent for research is NOT allowed in California.

13.2 AREAS OF RESEARCH: Is this study related to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of the research subjects:

(•) Yes

13.3 JUSTIFICATION: Explain why use of surrogates is necessary for completion of this study:

Secondary dystonia often causes significant problems with expressive language and speech as well as writing, and thus some subjects may not be able to give verbal or written consent.

13.4 COGNITIVE ASSESSMENT: Describe the plans for assessing the decision-making capacity of prospective subjects:

Baseline Neuropsychological testing will be performed as will make use of non-verbal testing methods to assess intellectual capacity and function of each subject. We will also rely on caregiver reports and the individual education plan (IEP) that is used by the schools to provide child specific instruction to fully understand each subjects abilities and deficits.

13.5 POST-ENROLLMENT CONSENT PLANS: Describe the plans for obtaining consent from subjects who regain ability to consent after a surrogate has given initial consent:

It is possible that the treatment with DBS will improve motor functioning enough to allow for a subject to provide either verbal or written consent during the post-operative follow-up. If this happens, we will reconsent the subject under his/her own capacity.

13.6 SURROGATE CONSENT REQUIREMENTS: Check to acknowledge:

☑ Research takes place in California. All surrogates will complete the "Self-Certification of Surrogate Decision Makers for Participation in Research" form.

☑ Conscious subjects will be notified of the decision to contact a surrogate. If subjects object to study

participation, they will be excluded even if their surrogate has given consent.

- [x] Surrogates will not receive any financial compensation for providing consent.
- [x] If a higher-ranking surrogate is identified at any time, the investigators will defer to the higher-ranking surrogate's decision regarding the subject's participation in the research.

For research taking place outside of California, explain how investigators will confirm that surrogates are legally authorized representatives:

N/A

14.0 Risks and Benefits

14.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- [x] For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- [ ] Risks associated with radiation exposure for imaging studies specifically for research purposes
- [ ] Risks associated with the administration of contrast agent for imaging studies
- [ ] Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- [ ] For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- [ ] For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- [ ] Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- [x] Risk of pain or physical discomfort caused by the research intervention
- [ ] Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

* For any boxes checked above, describe how you will minimize these risks and discomforts, e.g., adding or increasing the frequency of monitoring, additional screening to identify and exclude people with diminished kidney or liver function, or modification of procedures such as changing imaging studies to avoid giving contrast agent to people who are more likely to suffer side effects from it, etc.: **(REQUIRED)**

- Weight gain or cognitive impairment. This is a theoretical risk based on side effects reported from thalamotomies in prior research reports
- Stimulation induced dysarthria or weakness. This is a theoretical risk based on side effects reported from thalamatomies in this patient population. If these side effects occur, decreasing or turning off stimulation should eliminate them.
- Infection: We anticipate that the infection rate in this patient population may be higher than the infection rate in Parkinson's disease, Essential Tremor, and primary dystonia. This is due to known higher infection rates in children compared with adults and the presence of a mixed movement disorder with a greater amount of hyperkinetic movements as compared with other movement disorders patients.
- Patient growth necessitating lead/extension length revision
- Patient brain/skull growth leading to lead migration: In cases where growth of the brain and/or skull is not complete at time of implant, the distance from the lead anchor point (burr hole) to the target site increases with time and growth of the individual. As a result, lead migration relative to the target site may occur.
- Children should be advised to avoid games, sports and other pastimes where a strain to the lead /connector assembly or a percussive injury to system components may be likely to occur (e.g., soccer, football/rugby).
- Intracranial hemorrhage

- Hemiplegia/Hemiparesis
- Paresis/asthenia
- Worsening of Motor Impairment
- Trouble swallowing
- Sensory Impairment (e.g., pain, paresthesia, sensory disturbance, hypesthesia, hearing/tinnitus)
- Headache
- Speech/Language disturbances (e.g., dysarthria, hypophonia)
- Subcutaneous Hemorrhage/Seroma
- Cerebral Spinal Fluid Abnormality
- Eye visual disturbances (e.g., diplopia, abnormal vision, visual field defect) and eye disorders (e.g., twitching)
- Cognitive disturbances (e.g., thinking abnormal, confusion, alteration of mentation) and Neuropsychological disturbances (e.g., depression, anxiety)

14.2 RISKS: Describe any anticipated risks and discomforts not listed above:

Potential Risks

General risks of DBS surgery (risks incurred by any patient having DBS implantation surgery, within or outside of this protocol)

General Anesthesia

There are always risks with general anesthesia. This may include a reaction to medications, myocardial infarction, or even death. There may be unknown risks.

Risks of the surgical procedure

Implanting the neurostimulator system carries the same risks associated with any other brain surgery. Risks may include:

- Paralysis, coma, and/or death
- Bleeding inside the brain (stroke)
- Leaking of fluid surrounding the brain
- Air embolism (air bubble that enters an exposed blood vessel on the surface of the brain or in the skull bone, which can travel to the heart and possibly lung, a potentially life-threatening condition)
- Seizures
- Infection
- Allergic response to implanted materials
- Temporary or permanent neurological complications, including but not limited to decline in mental status, problems with speech, problems with movement or coordination
- Confusion or attention problems
- Pain at the surgery sites
- Headache

- Changes in hearing

Possible Device Complications

- There may be pain, lack of healing, or infection where the brain stimulation system parts are implanted. If this happens, further surgery or removal of part of the system may be necessary.
- The brain's stimulation system parts may wear through the skin which can cause an infection or scarring.
- The brain leads or lead/extension connectors may move. Further surgery to re-adjust the location may be needed.
- Components or parts of the brain stimulation system may suffer mechanical breakage resulting in loss of therapy. Further surgery to replace the system parts may be needed.
- The brain stimulation system could stop because of an electrical or software malfunction, which could require further surgery if noninvasive attempts to restore the software did not succeed.
- Battery in the pulse generator could be prematurely depleted. This would require further surgery. Pulse generator battery service life depends on individual use, but for most patients this should be > 2 years.
- There may be an allergic reaction to the brain stimulation system. The system materials coming in contact with the tissues include titanium, polyurethane, silicone, and nylon. The body could also reject the system (as a foreign body).
- There is the possibility of tissue damage resulting from the programming parameters or a malfunction of one of the parts of the brain stimulation system.

14.3

MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study**
- **having a plan for evaluation and possible referral of subjects who report suicidal ideation**

General Anesthesia. An attending pediatric anesthesiologist will administer and monitor the patient during the administration of all anesthesia and will be present during surgery.

Risks of the surgical procedure. Surgical risks will be minimized by utilizing a highly skilled surgical team that has performed over 1500 DBS device implants over the last 17 years. All procedures will be performed by a neurosurgeon specializing in DBS surgery who has personally performed over 1000 of these operations, at least 100 of which have been in children, which is one of the largest pediatric cohorts in the world. The study will exclude participants with major comorbidity increasing the risk of surgery (prior stroke, severe hypertension, severe diabetes, or need for chronic anticoagulation other than aspirin). After surgery, the patients will be admitted to a pediatric intensive care unit or neurosurgical transitional care unit and monitored for any postoperative complications. These specialized units have managed over 1000 postoperative DBS patients. All patients will be monitored for bleeding and other neurological changes related to the device or the surgical procedure.

Possible hardware related complications. The UCSF Surgical Movement Disorder Center has published extensively on risk avoidance, and risk management in patients undergoing DBS hardware implantation.[16,17] These include having participants wash with an antibacterial soap the evening prior to surgery, administration of an intravenous anti-staphylococcal cephalosporin with good skin penetration in the hour prior to incision, use of hair clippers only rather than razors, use of appropriate device anchoring techniques to underlying bone and fascia, creation of bone troughs to lower device profile in patients with thin skin, use of incisions that do not overlie the largest hardware diameter, multilayer closure, use of occlusive dressings, and wound inspection /staple removal by our own team, rather than an outside physician unfamiliar with device surgery, 10-14 days post-procedure.

Stimulation induced dysarthria or weakness: This is a theoretical risk based on side effects reported from thalamatomies in this patient population. If these side effects occur, decreasing or turning off stimulation should eliminate them.

Infection: We plan to increase the peri-operative antibiotic coverage to include methylcillin-resistance staphylococcus. Additionally, we will add a 10 day post-operative course of oral antibiotics to our infection prevention regimen as this has been suggested to improve post-operative infection rates in these children.

Depression: As part of screening and recording of adverse events at each interim visit, we will ask the patient and/or caregiver if the patient has experienced mood changes. In the event of severe worsening of mood and/or suicidal ideation, the study doctor will refer to appropriate psychiatry services, urgently consult with the medical safety monitor and log as an SAE.

Speech: As part of screening and recording of adverse events at each interim visit, the subject and caregiver will be asked about speech changes. Speech will also be assessed as part of dystonia rating scales by the study team. If there are negative changes detected on either AE recording or dystonia rating scales, the DBS will be turned off briefly to determine if these changes are stimulation induced. If these changes are not resolved with programming adjustment, the formal speech testing done initially on neuropsychological testing will be repeated, and this will be recorded as an AE.

Cognitive Changes: As part of screening and recording of adverse events at each interim visit, if the patient or caregiver endorses subjective cognitive changes, neuropsychological testing will be repeated. If there are negative changes on neuropsychological testing that cannot be resolved by stimulation changes, the study doctor will consult with the medical safety monitor.

Weight gain: Body mass index (BMI) will be measured at every visit and monitored for changes. Changes to BMI that are not attributable to improvement in the patient's condition or normal growth will be logged as an adverse event.

Additional time: Study visits will be conducted in conjunction with usual clinical visits, when possible, to minimize the amount of extra time needed to participate in the study

14.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

- **the proximity of an emergency facility for care of participant injury**
- **availability of psychological support after participation**
- **resources for participant communication, such as language translation services**

Both Investigators, study coordinators and clinical study staff are experienced in the conduct of human research and adept at maintaining safety, confidentiality and clinical care for patients enrolled in clinical trials. Each study role has back-up staff to insure availability and continuity of care.

14.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [x] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [ ] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [ ] Health and lifestyle changes may occur as a result of participation
- [ ] Knowledge may be gained about their health and health conditions
- [ ] Feeling of contribution to knowledge in the health or social sciences field
- [ ] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [ ] Other benefit (describe below)

☐ None

14.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

There are very few options for treating secondary dystonia, and most of the options are medications that carry very significant side effects, especially sedation. The potential of both reducing medications, improving quality of life, improving ability to function independently is worth the signficant risk that this study proposes.

15.0 Data and Safety Monitoring Plan

15.2 * DATA AND SAFETY MONITORING PLAN: (REQUIRED)

All greater than minimal risk studies are required to provide a plan. Lack of an adequate plan is one of the most common reasons why IRB approval is delayed.

Instructions:

Describe the plan for monitoring data quality and participant safety. Key areas that should be included in the plan are:

- An explanation of the plan to monitor data collection, study progress, and safety
- A description of who will perform the monitoring and at what frequency (e.g., the PI only, a contract research organization, a Data and Safety Monitoring Board or Data Monitoring Committee, etc.)
- The type of data and events that will be reviewed (e.g., adverse events, breaches of confidentiality, unanticipated problems involving risk to participants or others, unblinded efficacy data, etc.)
- Procedures and timeline for communicating monitoring results to the UCSF IRB, the study sponsor, and other appropriate entities
- Assurance that the research team will adhere to the **UCSF IRB reporting requirements**

As appropriate:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study interventions

The study participants will be followed bi-monthly for the first year and then as frequently as clinically indicated for the second year. Safety assessments will be done at every visit including vital signs, limited physical exam, safety check of the DBS device. Any Adverse Experience will be recorded and the subject diary will be reviewed to detect any adverse experiences. The Investigator will maintain constant vigilance over the study and review the data no less than on a monthly basis. The data will be presented and reviewed by the MSM at least every 6 months. Data will be presented and reviewed by the IRB annually.

Study stopping criteria are two or more patients with study related serious adverse events i.e. symptomatic intracranial hemorrhage, subdural hematoma, seizures, worsening neurological status, or death.

Subject stopping criteria would be (1) greater than 40% worsening on the Burke-Fahn-Marsden dystonia rating scale (BFMDRS) or the Barry Albright dystonia scale (BADS) that does not improve with programming changes (2) Depression that does not improve with programming changes or suicidiality. Any patient that is withdrawn from the study will be followed as part of intention to treat analysis.

15.3 * DATA AND SAFETY MONITORING BOARD (DSMB): Will a Data and Safety Monitoring Board (DSMB) be established: (REQUIRED)

- (•) Yes
- ( ) No

15.4 DSMB DETAILS: Provide details from the DSMB's charter, including meeting frequency, and affiliations and qualifications of members: If the DSMB has not yet been established, submit these details to us as they become available.

All AEs will also be reported to the, medical safety monitor (MSM) who is a neurosurgeon (Dr. Paul Larson) within the institution with no direct involvement in this study but who have expertise in implantable devices. Treatment related adverse events assessed as definitely, probably, or possibly related to study procedures and either serious or unexpected, noted by any study personnel will be reported within 5 working days of their knowledge of the event to the MSM. The MSM will then advise the PI on potential changes in procedures to improve safety, or, in the event of multiple serious adverse events, may invoke stopping rules.

16.0 Confidentiality, Privacy, and Data Security

16.1 PROTECTING PRIVACY: Indicate how subject privacy will be protected:

- [x] Conduct conversations about the research in a private room
- [x] Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- [x] Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission
- [ ] Other methods (describe below)

16.2 SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior:

( ) Yes (•) No

16.3 CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation:

( ) Yes (•) No

16.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

Data will be stored in a computerized spreadsheet with identifiers removed and information anonymized when entered into the file. The link between identifying information (i.e., subject's full name) and the research code will be stored in an encrypted database. Computer-based files will only be made available to personnel involved the study through the use of access privileges and passwords.

The database portal can be accessed only from the UCSF Surgical Movement Disorders offices and from other approved locations with VPN access and authenticated by the database manager.

De-identified patient data may be transmitted and received via secure network with other movement disorders centers. Patient data will include demographics, clinical history, surgical data, clinical scales (for example, Burke-Fahn-Marsden and Barry-Albright Dystonia scales), surgical complications, medication information, and programming data.

16.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others: (REQUIRED)

○ Yes ◉ No

16.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obain a Certificate of Confidentiality:

○ Yes ◉ No

16.7 SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers:

◉ Yes ○ No

Note: This is unusual and not recommended, particularly in cases where the tests are carried out in a non-CLIA certified laboratory, the results are of unproven clinical significance, or where there are not known preventative strategies and/or treatments. If these are the most likely scenarios for your study, you should check 'No.'

If you have an incidental finding of clear clinical significance, call the HRPP QIU at 415-476-1814 for a consult.

Explain under what circumstances research results may be shared:

Results of Neuropsychological testing will be shared with the subject and caregivers and they will be counseled on the results.

16.8 * IDENTIFIERS: Will any personal identifiers be collected: (REQUIRED)

◉ Yes ○ No

Check all the identifiers that may be included:

- ☑ Names
- ☑ Dates
- ☑ Postal addresses
- ☑ Phone numbers
- ☐ Fax numbers
- ☑ Email addresses
- ☑ Social Security Numbers*
- ☑ Medical record numbers
- ☑ Health plan numbers
- ☐ Account numbers
- ☐ License or certificate numbers
- ☐ Vehicle ID numbers
- ☐ Device identifiers or serial numbers
- ☐ Web URLs

- [ ] IP address numbers
- [ ] Biometric identifiers
- [x] Facial photos or other identifiable images
- [ ] Any other unique identifier

If publications from this study may include ANY photos or images of patients - even without faces - either collected for research or from the medical records, you are required to have each patient sign the 'Consent for Photography / Authorization for Publication' form prior to submittal for publication. Failure to obtain consent for publication may result in a finding of Serious Non-compliance by the IRB and civil and criminal penalties, *including fines up to $1.5 million dollars* for violation of the HIPAA privacy protections if a participant complains.

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

- (•) Yes
- ( ) No

16.9 DATA DISCLOSURE: Will identifiable information be shared with outside groups:

- ( ) Yes
- (•) No

16.11 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- [x] Paper-based (surveys, logs, diaries, etc.)
- [x] Electronic case report forms (CRFs), such as OnCore or another clinical trial management portal
- [ ] Web-based online surveys or computer-assisted interview tool
- [ ] Mobile applications (mobile or tablet-based)
- [ ] Wearable devices
- [x] Audio/video recordings
- [ ] Other:

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

- [x] UCSF
- [ ] SF VAMC
- [ ] Amazon (Amazon Cloud)
- [ ] Other academic institution
- [ ] 3rd party vendor (business entity)
- [ ] Other (explain below)

16.12 DATA SECURITY: Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- [x] Data are stored securely in My Research
- [ ] Data are coded; data key is destroyed at end of study
- [x] Data are coded; data key is kept separately and securely
- [ ] Data are kept in a locked file cabinet
- [x] Data are kept in a locked office or suite

- [x] Electronic data are protected with a password
- [x] Data are stored on a secure network
- [ ] Data are collected/stored using REDCap or REDCap Survey
- [ ] Data are securely stored in OnCore

16.13 * DATA SECURITY: Confirm below that you will keep data confidential: (REQUIRED) I will keep any data sets that include identifiers secure and protected from improper use and disclosure by using methods such as:

- **Physical Security – Keeping data in locked file cabinets, locked offices, locked suites, and physically securing computers and servers.**
- **Electronic Security – Following UCSF minimum security standards for electronic information resources, which includes (but is not limited to): not storing identifiers on portable devices like laptops or flash drives if they are unencrypted, encrypting portable devices, and storing data in password-protected files and on secure networks.**

- (•) Yes

16.15 HIPAA APPLICABILITY: Study data will be:

- [ ] Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
- [x] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [x] Added to the hospital or clinical medical record
- [x] Created or collected as part of health care
- [x] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained ONLY from a foreign country or countries
- [ ] Obtained ONLY from records open to the public
- [ ] Obtained from existing research records
- [ ] None of the above

Unless a waiver of Authorization is granted, in addition to the consent form, participants will need to sign UCSF Research Subject Authorization Form (HIPAA Form). NEW REQUIREMENT - This form should be uploaded in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to obtain HIPAA Authorization for research is one of the most common findings from QIU Routine Site Visits. Your IRB approval letter will include instructions about HIPAA requirements specific to your study.

If derived from a medical record, identify source:

APEX, records sent from outside providers

16.16 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)

- [ ] Drug or alcohol abuse, diagnosis or treatment
- [ ] HIV/AIDS testing information
- [ ] Genetic testing information
- [ ] Mental health diagnosis or treatment
- [x] None of the above

17.0 Financial Considerations

17.1 * PAYMENT: Will subjects be paid for participation, reimbursed for time or expenses, or receive any other kind of compensation: (REQUIRED)

(•) Yes ( ) No

17.2 PAYMENT METHODS: Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [ ] Cash
- [ ] Check
- [ ] Gift card
- [ ] Debit card
- [ ] UCSF Research Subject Payment Card
- [x] Reimbursement for parking and other expenses
- [ ] Other:

17.3 PAYMENT SCHEDULE: Describe the schedule and amounts of payments, including the total subjects can receive for completing the study:

- **If there are multiple visits over time, explain how payments will be prorated for partial completion**
- **If deviating from recommendations in Subject Payment Guidelines, include specific justification below**

17.4 COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

(•) Yes ( ) No

Describe the costs that may be incurred by subjects or 3rd party payers as a result of participation:

- Explain why it is appropriate to charge those costs to the subjects
- If this is a therapeutic study, compare subjects' costs to the charges that would typically be associated with receiving care off-study (e.g. is it more expensive to participate in this study than to receive care off-study?)

Although the goals of the study are to assess safety and tolerability, the secondary are to treat the subject's dystonia with an approved medical device that we are using off-label (with an IDE) for this patient population. Inclusion criteria specify that there are no other treatment options available to the participants. When we obtain authorization from the subjects insurance carrier for implantation of the DBS device, we will also verify that the subject's insurance will also provide coverage for any possible explantation of the device.

18.0 Qualifications of Key Study Personnel

18.1 NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Also identify each person who will be

involved in the consent process. Click the orange question mark for more information and examples. **Under qualifications, please include:**

- **Academic Title**
- **Institutional Affiliation (UCSF, SFGH, VAMC, etc.)**
- **Department**
- **Certifications**

November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website.**

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
Dr. Ostrem, Jill M.D.	As study investigator, Dr. Ostrem will help interpret and analyze the data.	Dr. Ostrem is fellowship trained in movement disorders, board certified in Neurology and an Associate Professor of Neurology at UCSF. She has extensive clinical and research experience in the area of medical and surgical movement disorders.
Dr. Starr, Philip MD, PhD	Dr. Starr will perform study neurosurgical procedures and participate in evaluation of study data.	Dr. Starr is board certified in neurosurgery, fellowship trained in movement disorders surgery, board certified in neurosurgery, and a Professor of Neurosurgery at UCSF. He has performed >800 deep brain stimulator implants for movement disorders and is one of the most experienced functional neurosurgeons in the world. He has published extensively on deep brain stimulation and dystonia physiology.
Volz, Monica M	As study nurse, Ms. Volz will consent patients, manage and program study patients and record data.	Monica Volz, MS, RN, is a clinical nurse specialist with 10 years of experience managing clinical trials and movement disorders patients treated with deep brain stimulation.

Dr. Demopoulos, Carly PhD	As study neuropsychologist, Dr. Demopoulous will administer neuropsychological testing and help interpret results.	Dr. Demopoulous has a Ph.D. in neuropsychology with fellowship training. She has special expertise in testing children with communication difficulties.
Racine, Caroline	As a study investigator and neuropsychologist, Dr. Racine will help interpret with results of neuropsychological testing.	Dr. Racine is an experienced clinical neuropsychologist at UCSF with special expertise in movement disorders.
Dr. San Luciano Palenzuela, Marta M.D., MD	As study P.I., Dr. San Luciano will be responsible for overseeing the study, recruiting subjects, evaluating and examination of subjects, recording data, and data analysis and interpretation.	Dr. San Luciano is an Assistant Clinical Professor of Neurology at UCSF and is fellowship- trained in movement disorders and has experience in DBS.
Larson, Paul S, MD	Dr. Larsen will serve as the neurosurgeon on the Data Safety Monitoring Committee	Dr. Larsen is board certified in neurosurgery, board certified in neurosurgery, and a Professor of Neurosurgery at UCSF. He is one of the most experienced functional neurosurgeons in the world. He has published extensively on deep brain stimulation.
Wang, Sarah S	Dr. Wang will help with project logistics and help provide regulatory oversight and CHR requirements.	Dr. Wang is a Senior Research Coordinator in the UCSF Surgical Movement Disorders Center.
Watson, Christa L	As study neuropsychologist, Dr. Watson will administer neuropsychological testing and help interpret results.	Dr. Watson has a Psy D and is a post doctoral fellow at the Dyslexia Center at UCSF. She has special expertise in working with pediatric patients.
Gittings, Melissa L	As a research coordinator, Melissa will work on data entry, data reporting, and other regulatory responsibilities.	Melissa is a clinical research coordinator in the UCSF Movement Disorders and Neuromodulation Center.
Dr. Bledsoe, Ian MD	As study investigator, Dr. Bledsoe will help interpret and analyze the data.	Dr. Bledsoe is an Assistant Clinical Professor of Neurology at UCSF and is fellowship-trained in movement disorders and has experience in DBS.
Viser, Aaron	As a research coordinator, Aaron will work on data collection through chart review, data verification, and manuscript preparation.	Aaron is a clinical research coordinator in the UCSF Movement Disorders and Neuromodulation Center.

19.0 Other Approvals and Registrations

19.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects (Help Link added Aug '15):

(REQUIRED)

○ Yes ◉ No

19.2 * HUMAN GENE TRANSFER: Does this study involve human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to IRB approval): (REQUIRED)

○ Yes ◉ No

19.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

20.0 End of Study Application

20.1

End of Study Application Form

To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and Save and Continue through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections. Once you are sure the form is complete, click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB wants your feedback about this new form. Please click the link to take a brief survey about the new application form.