CLINICAL TRIAL PROTOCOL

PI Name: Kristina Simonyan, MD, PhD, DrMed

Protocol Title: Sodium oxybate in spasmodic dysphonia and voice tremor

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FDA IND: 11,7954

IRB protocol: 2019P001680

Sponsor: NIH-NIDCD National Institute on Deadness and Other Communication Disorders

1. STUDY SUMMARY

Provide a brief summary of the proposed research (in language that can be understood by a non-scientist).

Response: Spasmodic dysphonia, or laryngeal dystonia, is a chronic debilitating condition that selectively affects speech production due to involuntary spasms in the laryngeal muscles. SD often extends beyond vocal communication impairment and causes significant occupational disability and life-long social isolation. SD becomes even more incapacitating when it is associated with dystonic voice tremor (VT), which is present in about 1/3 of SD patients and is characterized by the inability to sustain a vowel for more than a few seconds. Current treatment of these disorders is limited to the temporary management of voice symptoms with repeated injections of botulinum toxin into the laryngeal muscles, which, however, are not effective in all SD patients and even less so in combined SD/VT cases. There is, therefore, a critical need to identify alternative therapeutic options that are specifically targeting the pathophysiology of SD and VT. On the other hand, the design and use of such novel therapeutic approaches will be largely unattainable if their central mechanisms of action remain unknown. Our long-term goal is to determine the pathophysiology of SD and related disorders, such as VT, and develop new diagnostic and treatment options for these patients. The objective of this application is to elucidate the primary determinants of clinical response to a novel oral medication, sodium oxybate (Xyrem®), in alcohol-responsive SD and SD/VT patients. This research is innovative because it will use a controlled experimental design that focuses on detailed characterization of primary effects of a novel oral medication, sodium oxybate, for treatment of SD and VT symptoms. The proposed research is significant because it is expected to have broad translational impact on improving the clinical management of patients with SD and VT, opening new therapeutic horizons for treatment of these and similar disorders.

2. SPECIFIC AIMS

List the specific aim(s) and objective (s) of the study (i.e., what does the study hope to accomplish). Include any secondary and exploratory aims and objectives (e.g., biomarkers, genetic analyses).

Response: Determine the clinical response of SD and VT symptoms to sodium oxybate.

3. BACKGROUND AND SIGNIFICANCE

Describe the scientific background and rationale for the study.

- Provide a critical review of the relevant literature and the state of current knowledge on the topic. Discuss deficiencies or gaps in knowledge that make the study worth doing. Include a list of literature cited in an appendix at the end of this protocol.
- Discuss the importance of the topic with respect to scientific knowledge, clinical practice, public health, impact on individuals/community, incidence, prevalence, mortality and morbidity, as applicable.

Response: SD develops in midlife and progresses to become a chronic debilitating condition, which impacts nearly every aspect of a patient's life, causing emotional stress, loss of employment, social embarrassment, and isolation. About 1/3 of SD patients develop so-called dystonic VT, which affects a dystonic body part (i.e., the larynx) and additionally challenges patient's already impaired vocal communication (Kirke et al., 2016). Clinically, the presence of VT in SD patients complicates the accuracy of diagnosis due to the similarities between symptoms of these disorders and shows a poor, if any, response to botulinum toxin treatment (Sulica and Louis, 2010; Gurey et al., 2013). On the other hand, SD symptoms can be managed only temporarily with botulinum toxin injections, although this treatment is not effective in all SD patients (Ludlow et al., 2008; Novakovic et al., 2011). In the clinical setting, a minority of SD and VT patients receive off-label oral medications, such as propranolol, primidone, clonazepam and lorazepam, which, however, provide only mild benefits (Adler, 2000). Other treatment approaches specifically targeting the pathophysiology of these disorders have not been established, leaving a large portion of patients to rely on short-term, and often suboptimal, management of their symptoms with botulinum toxin injections or even remain untreated.

One of the main reasons for the paucity of novel therapeutic options to treat SD and VT is our incomplete understanding of their *pathophysiology with respect to treatment outcome*. Recent studies by us and others identified SD-characteristic brain functional alterations in the laryngeal sensorimotor cortex, parietal cortex, basal ganglia, thalamus, and cerebellum (Haslinger et al., 2005; Ali et al., 2006; Simonyan and Ludlow, 2010, 2012; Battistella et al., 2016; Termsarasab et al., 2016; Waugh et al., 2016), proposing that SD, similar to other forms of focal dystonia, may represent a large-scale functional network disorder (Battistella et al., 2015). We further identified an extensive overlap between SD and VT functional brain abnormalities, suggesting a similarity of their pathophysiological mechanisms (Kirke et al., 2016). Moreover, common to both SD and SD/VT patients, the severity of voice symptoms correlated with increased brain activity in the putamen and inferior frontal gyrus (Simonyan and Ludlow, 2010, 2012; Battistella et al., 2016; Kirke et al., 2016), suggesting that functional abnormalities in these disorders may be similarly targeted by novel therapeutic options. Taking into account their clinical phenomenology, we found that one of the common clinical traits of SD and VT is the responsiveness of their symptoms to alcohol (Kirke et al., 2015). Thus, by targeting these shared clinical and pathophysiological features of SD and VT, we showed that sodium oxybate (Xyrem®), an oral medication that mimics effects of alcohol, was successful in significantly ameliorating voice symptoms in 82% of alcohol-responsive (ETOH+) patients through direct modulation of abnormal sensorimotor, putaminal and cerebellar brain activity (Simonyan and Frucht, 2013; Kirke et al., 2015; Rumbach et al., 2016). Sodium oxybate is chemically identical to gamma-hydroxybutyric acid (GHB), a naturally occurring inhibitory neurotransmitter (Waszkielewicz and

Bojarski, 2004); it converts into GABA within the brain (Crunelli et al., 2006) and increases dopamine levels mediated by $GABA_B$ receptors (Gessa et al., 2000; Snead and Gibson, 2005; Keating, 2014). Our current state of knowledge of dystonia pathophysiology suggests that, following its conversion into GABA in SD and SD/VT patients, sodium oxybate likely modulated abnormal brain activity through normalization of the altered balance between excitation and inhibition (Perlmutter et al., 1997; Garibotto et al., 2011; Quartarone and Hallett, 2013; Simonyan et al., 2013), leading to reduction of dystonic symptoms. Thus, based on these data, *we anticipate that sodium oxybate may be among the first potent oral medications for treatment of ETOH+ SD and VT that selectively targets the underlying disorder pathophysiology.* The drug's benefits will potentially be seen in a large cohort of SD and VT patients because (1) alcohol responsiveness is a common clinical phenomenon in these disorders (Kirke et al., 2015), and (2) improvement of voice symptoms following administration of sodium oxybate is observed in the vast majority of ETOH+ SD and SD/VT patients (Rumbach et al., 2016).

Our initial findings in SD and SD/VT patients are reliable because prior studies of sodium oxybate in patients with various other ETOH+ movement disorders have similarly established satisfactory tolerability and over 50% symptom improvement (Frucht et al., 2005a; Frucht et al., 2005b; Arpesella et al., 2009). However, all these studies have been conducted using an open-label experimental design based on patients' subjective reports of alcohol effects on their symptoms. Likewise, our initial examination of central effects of sodium oxybate in SD and SD/VT patients has also followed an open-label study design. As a consequence, a placebo effect of the drug cannot be ruled out. It is, therefore, critical to perform a standardized test of alcohol challenge for robust stratification of patients into ETOH+ group and conduct a double-blinded, placebo-controlled, randomized, crossover study in order to validate our initial findings of sodium oxybate treatment response and delineate its central effects in ETOH+ SD and SD/VT patients.

Significance of the Expected Research Contribution. Our contribution here entails the detailed understanding of the primary contributing factors that underlie the clinical benefits of sodium oxybate in ETOH+ SD and SD/VT patients. Our rigorous experimental approach will include symptom evaluation based on the objective alcohol challenge test and double-blind, placebo-control, randomized, cross-over study design to identify the primary determinants of sodium oxybate response in ETOH+ SD and SD/VT patients. The expected outcome of these studies will allow for translations from bedside to bench and bedside again, maximizing integration between clinical and basic aspects of this research program. Collectively, the proposed studies have strong scientific premise because they will allow for delineation of the mechanistic aspects of sodium oxybate's effects on SD and VT pathophysiology. As such, successful completion of the proposed studies will establish a much-needed scientific rationale for the future large clinical trials and the ultimate use of sodium oxybate as a therapeutic option for treatment of SD and VT. This will be especially important for those patients who have suboptimal response to botulinum toxin treatment or forgo it due to personal or medical issues. *Thus, this contribution will be significant because it is expected to have a broad translational impact on improving the clinical management of patients with SD and VT.* It is further expected that our findings will be equally applicable to the treatment of other forms of ETOH+ dystonia and dystonic tremor. Taken together, the proposed rigorous experimental approach to identify an effective oral medication for SD and SD/VT based on disorder pathophysiology will represent a significant departure from the existing trial-and-error attempts to treat these disorders. It will represent a novel therapeutic approach directed to the treatment of the *disorder per se* rather than temporary management of voice symptoms as with the current use of botulinum toxin.

4. STUDY DESIGN

Provide a detailed description of the study design (e.g. cross-sectional, stratified, longitudinal, prospective cohort, case-control, randomized, placebo-controlled, masked/double masked, feasibility, pilot, proof-of-concept, etc.).
Explain why this study design is appropriate for this study.

Response: We will employ a double-blind, placebo-controlled, randomized, cross-over study to objectively determine the clinical response to sodium oxybate in ETOH+ SD and SD/VT patients compared to patients with ETOH- SD and SD/VT.

5. SUBJECT INFORMATION

a) Target Enrollment- Specify the number of subjects you plan to enroll and justify why this number is sufficient to achieve adequate power for statistical analysis taking into account anticipated screen failures and drop-outs. Include sample size by cohort if the study has multiple cohorts.

Response: Specific Aim #1: To estimate the number of patients in this study, we reviewed our open-label study, in which sodium oxybate improved voice symptoms in 82.2% (37 out of 45) of ETOH+ SD and SD/VT patients ($p = 0.001$). To our knowledge, no other studies have examined the benefits of sodium oxybate in SD and SD/VT. Using an estimated effect size based on values from this study, a binomial test found that a power of 80% at a significance level of 0.0125 will be obtained with 22 patients for the proposed study. To account for a potential patient dropout based on our prior study, we will recruit up to 35 patients per cohort. The total of recruited patients will be up to 140 (4 cohorts x 35 patients/cohort).

b) If this is a multi-center study and other sites rely on the MEE HSC as the IRB of record, please specify the total number of subjects required by all sites to achieve sufficient power.

Response: N/A

c) Provide justification that the researchers have access to sufficient numbers of eligible subjects to meet target enrollment goals (e.g., researcher's own patients, clinic patients with a specific diagnosis, subjects from previous studies who agree to participate in future studies).

Response: Our research team has access to all patients with dystonia seen at MEEI and MGH/Neurology. All potential subjects will be screened for study participation. Based on our previous experience and studies, our estimation is that about 70% of patients with dystonia may be eligible for participation in this study. In addition, patients will be recruited through the advertisements in the newsletters and websites of the National Spasmodic Dysphonia Association (NSDA) and Dystonia Medical Research Foundation (DMRF), and MEEI flyers. Healthy volunteers can be non-blood relatives of patients. Participants' self-referral will be allowed. Patients seen at MEEI will be asked if they would consider participating in the research study. Subjects from previous studies who agreed to participate in future studies (N~300) will be contacted and screened for eligibility. If the patient is interested, the study purposes and procedures will be explained. If the patient will be willing to participate in the study, he/she will be given the contact information of the

PI and the research team for further information and scheduling of the study procedures. We do not expect any major challenges associated with subject recruitment.

6. ELIGIBILITY CRITERIA

a) Inclusion Criteria - Inclusion criteria are the specific characteristics of the study population(s) required for study enrollment (e.g., ages, gender, condition or disease.) List the inclusion criteria in a bulleted list.

Response**:**

1. SD and SD/VT patients will have clinically documented ADSD or ABSD with and without positive effects of alcohol on their symptoms;
2. Age from 21 to 80 years.
3. Native English speakers.
4. Right-handedness (based on Edinburgh Handedness Inventory).

b) Exclusion Criteria - Provide specific criteria for determining ineligibility to participate. Provide justification for their exclusion (e.g., pregnant women).

Note: Exclusion criteria are not always clinical in nature. Exclusion may also include circumstances that interfere with:

- the participant's ability to give informed consent (diminished cognitive capacity or a language other than English and an interpreter unavailable)
- contraindications to the study treatment(s)/procedure(s)
- taking certain concomitant medication(s) or
- conditions that interfere with a patient's ability to comply with all study procedure(s*)*

Response**:**

1. Subjects who are incapable of giving an informed consent will be excluded from the study.
2. Pregnant and breastfeeding women until a time when they are no longer pregnant, or breastfeeding will be excluded from the study. All patients of childbearing potential will be required to agree to use a reliable method of contraception prior to and during the study. The method of contraception will be documented in the patient's research chart. All women of childbearing potential will undergo a urine pregnancy test, which must be negative for study participation.
3. All patients with a past or present history of the following conditions will be excluded from the study;
    (a) Except for SD and dystonic VT, any neurological disorders, such as stroke, movement disorders, brain tumors, traumatic brain injury with loss of consciousness, ataxias, myopathies, myasthenia gravis, demyelinating diseases, drug dependence. Patients with tremor affecting other body parts will be excluded from the study. All patients who have dystonic movements in the body regions other than the larynx will be excluded from the study. This will allow maintaining the homogenous patient population and evaluating central drug effects without confounding by the presence of other neurological conditions.

(b) Any psychiatric problems, such as schizophrenia, major and/or bipolar depression, obsessive-compulsive disorder, will be excluded to maintain the homogenous patient population and allow for the evaluation of central drug effect without confounding by the presence of psychiatric conditions.
(c) Patients with a known past or present history of grade 2 or higher hepatic and renal dysfunction according to the NCI criteria will be excluded.
(d) Patients with a known past or present history of moderate to severe congestive heart failure will be excluded.
(e) Patients with a known past or present history of cognitive impairment and active suicidal ideations will be excluded.
(f) Patient with a known past or present history of alcoholism and/or at high risk for alcohol use disorder according to the NIAAA definition (women > 7 drinks per week or 4+ drinks daily; men >14 drinks per week or 5+ drinks daily) and DSM-5 criteria (with ≥2 symptoms indicate alcohol use disorder) will be excluded.

4. Patients who are not symptomatic due to treatment with botulinum toxin injections into the laryngeal muscles will be excluded from the study until the time when they are fully symptomatic. The duration of positive effects of botulinum toxin vary from patient to patient, lasting on average 3-4 months. All patients will be evaluated to ensure that they are fully symptomatic prior to the entering the study.
5. To avoid the possibility of confounding effects of drugs acting upon the central nervous system, all patients will be questioned about *any* prescribed or over-the-counter medications as part of their initial intake screening. Those patients who receive medication(s) affecting the central nervous system (except for sodium oxybate) will be excluded from the study.
6. Patients will be asked whether they have undergone any head and neck surgeries, particularly any brain surgery and laryngeal surgeries, such as thyroplasty, laryngeal denervation, and selective laryngeal adductor denervation-reinnervation. Because both brain and laryngeal surgery may potentially lead to the brain structure and function re-organization, all subjects with a history of brain and/or laryngeal surgery will be excluded from the study.
7. Patients who have tattoos, ferromagnetic objects in their bodies (e.g., implanted stimulators, surgical clips, prosthesis, artificial heart valve, etc.) that are not MRI comparable and/or cannot be removed for the purpose of MRI study participation will be excluded from the study (for follow-up study).

NOTE: Per federal regulations, the risks and benefits of research must be fairly distributed among the populations that could benefit from the research. No groups of persons (e.g., gender, pregnant women, children, minorities, non-English speakers) should be categorically excluded from research without a valid scientific or ethical reason to exclude such groups.

c) Describe your rationale that the study population is representative of populations that may potentially benefit from the research, or the rationale for excluding certain groups, if applicable.

Response**:** N/A

7. RECRUITMENT PROCESS

NOTE: HIPAA does not permit non-MEE physicians to disclose patient information to Mass Eye and Ear for research recruitment. Non-MEE physicians may inform their patients of a research study and allow the patients to self-disclose their interest to the MEE study team.

Provide a detailed description of the recruitment plan (consistent with information you provide in the PRA), who is responsible for recruitment, how and when subjects will be recruited (i.e., flyers, advertisements, letters and oral/telephone scripts, email, at clinic appointments, etc.). Note: The HSC must review all recruitment materials. Please upload these materials into IRBNet with this submission.

Response**:** Patient volunteers will be recruited through MEEI Laryngology and MGH Neurology, advertisements in the Dystonia Medical Research Foundation and National Spasmodic Dysphonia Association newsletters and on their websites, advertisements in the local patient support groups, contacts with referring physicians as well as from the large pools of patients who have previously participated in our studies or have been seen for treatment by our research and clinical teams. Participants will be recruited regardless of their race, sex, age, religion, or national origin.

We will minimize the possibility of patients feeling obligated to participate when recruited by the investigators' own patients in the following ways.
We may ask a physician colleague to initially explain the study or may contact the patient in writing. We may explain the study at the first encounter, give the opportunity to take home the Consent Form, and re-contact the potential patient or ask them to call us back about their willingness to participate. We may recommend that the patient discuss participation with other health care providers.

During the first contact, the purposes, procedures, and risks of the protocol will be described in non-technical language and preliminary information about the present voice problems will be obtained. If the patient expresses an interest in study participation, an appointment will be scheduled for the informed consent, after which he/she will be interviewed to review background medical information, including voice, speech, language, swallowing, hearing, breathing, neurological, psychiatric diseases and disorders. In addition, the neurological, laryngological and cognitive assessments may be performed at this time.

The study procedures will be arranged as follows:

- Initial screening to establish eligibility,
- Covid-19 test for detection of infection prior to study participation, if applicable
- Review of medical information
- Informed Consent
- Questionnaires and rating scales
- Voice and speech recordings
- Blood or saliva sampled
- Alcohol/sodium oxybate/placebo administrations
- Data analysis and interpretation

8. CONSENT PROCESS

a) 8a. Describe the consent process in detail. Include the following information:
   - who (e.g., physician, nurse, coordinator) will obtain consent,
   - their knowledge/experience in obtaining consent
   - location of the consent process
   - use of the Documentation of Consent Process Form
   - how the study information is presented (written consent form, orally, study information sheet, use of "short form" or translated consent etc.)
   - timing of consent (e.g., during pre-surgical visit, about one week before the screening visit)

Response**:** Consenting of patients will be done in a private room at MEEI Laryngology or MGH Neurology, with only research team members present. Subjects will be informed that they may choose not to answer a specific questions about their medical history, however, this may present one of the reasons for exclusion as determined by a research team. The PI or a licensed physician investigator, who have appropriate knowledge in obtaining consent, will obtain the consent. If consented by the PI, the consent of all subjects will be conducted at a time when a licensed MD on the research team is available either by phone or in person. Each subject will be offered the opportunity to have a conversation with a licensed physician, and the subject's decision will be formally documented. The General Research Consent and Authorization will be used to obtain written informed consent from all participants. All study procedures will be explained orally; all subjects will be given sufficient time to fully read the consent; all questions and concerns will be addressed before obtaining the subject's signature. Consent will be administered before any research procedures are performed.

b) 8b. How will you assess a subject's understanding of the research initially and over the course of the study? Is the presentation of study information appropriate for the study population (low vision, hearing impaired)? Describe specific provisions for subjects with limited understanding (e.g., a family member or other appropriate 3rd party is involved in the consent process).

Response**:** Subjects who are incapable of giving an informed consent will be excluded from the study. We will allocate sufficient amount of time on individual patient's basis to explain and answer all questions about the study procedures. We will ask questions to make sure the subjects understand the research study fully.

c) 8c. If the research-related intervention or interaction will occur on the same day that the subject initially receives information about the study, justify why this is appropriate/necessary.

Response**:** N/A

d) 8d. Describe provisions in place for non-English speaking subjects, including use of translators during the consent process and the translation of consent documents.

Response**:** Non-English speaking subjects will not be included into the study.

e) 8e. If a subject cannot read the consent form (e.g., low literacy, low or no vision) or cannot hear the person obtaining consent, explain how you will conduct the consent process and the provisions to accommodate subjects with limited or no hearing and/or limited or no vision.

Response**:** As impaired hearing, vision and speaking abilities most typically have neurological origins, these subjects will be excluded from the study.

9. STUDY PROCEDURES

a) Provide a detailed description of all study procedures and intervention(s) each subject and/or cohort will experience. Provide a schedule of visits and the procedures that occur at each visit (e.g., tests, questionnaires, surveys, imaging or other interventions.). If the study also involves standard of care, differentiate between research only procedures and standard of care.

Response**:**

Determine the clinical response of SD and SD/VT symptoms to sodium oxybate using a double-blind, placebo-controlled, randomized, cross-over study design.

The experimental design includes (1) screening for study eligibility; (2) an objective standardized alcohol challenge test for assessment of symptom responsiveness to alcohol, and (3) a double-blind, placebo-controlled, randomized, crossover study of sodium oxybate. The **primary outcome** will be to determine the response of SD and VT symptoms to sodium oxybate 40 min after administration, compared to placebo. We will recruit the following groups of patients:

(1) ETOH+ SD and SD/VT who report positive effects of alcohol on their voice symptoms;

(2) ETOH- SD and SD/VT who report no effects of alcohol on their voice symptoms, and

Although our prior studies have shown that sodium oxybate has similar effects in both SD and SD/VT patients as well as in ADSD and ABSD, the inclusion of these patients will allow to capture the entire SD populations and to cross-validate our findings. On the other hand, the inclusion of negative controls with ETOH- SD and ETOH- SD/VT will allow for enhanced explanations of our findings and delineation of the primary factors contributing to the pathophysiology of SD and VT with respect to treatment outcome.

Enrollment and Eligibility Screening. Patient eligibility will be established based on the initial screening interview and the review of medical information, including laryngological and neurological examinations. Any subject with neurological (other than SD or dystonic VT in the patient groups), laryngeal, or a history of psychiatric problems will be excluded from the study. All patients will be right-handed, native English speakers according to the standardized Edinburgh Handedness Inventory (Oldfield, 1971), which will be important in examining drug-induced central effects during speech production. Because brain and laryngeal surgery may influence functional brain organization, all patients with a history of brain and/or laryngeal surgery will be excluded from the study. To avoid the possibility of confounding effects of drugs that act upon the central nervous system, patients who receive any medication(s) affecting the central nervous system will be excluded from the study. All patients will be asked to abstain from consuming any alcohol or caffeine (or foods with caffeine such as chocolate) for at least 48 hours before the study visits.

General Study Procedures. Eligible patients will require three visits, including one for the alcohol challenge test and two for sodium oxybate and placebo treatments (**Fig. 1**). At their initial baseline, all patients will be assessed for vital signs (blood pressure, pulse, height and weight); cognitive and executive functions using the Montreal Cognitive Assessment (MoCA); prospective suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS), alcohol use disorder using NIAAA Recommended Alcohol Questions (Six Question Set) and DSM-5 Alcohol Use Disorder Questionnaire, daytime sleepiness using the Epworth Sleepiness Scale, voice/speech and dystonia symptoms (recordings and rating scales); blood will be sampled for genetic analysis. To reduce the burden to participants, some standardized assessments (Edinburgh handedness inventory) collected under the PI's other protocols within the last 12 months may be used in the same participants who agreed to the use of their data for other research studies. This will be done only in those participants who do not have any major changes in their health history at the time of intake screening for this study compared to the time when they participated in the PI's other protocols.

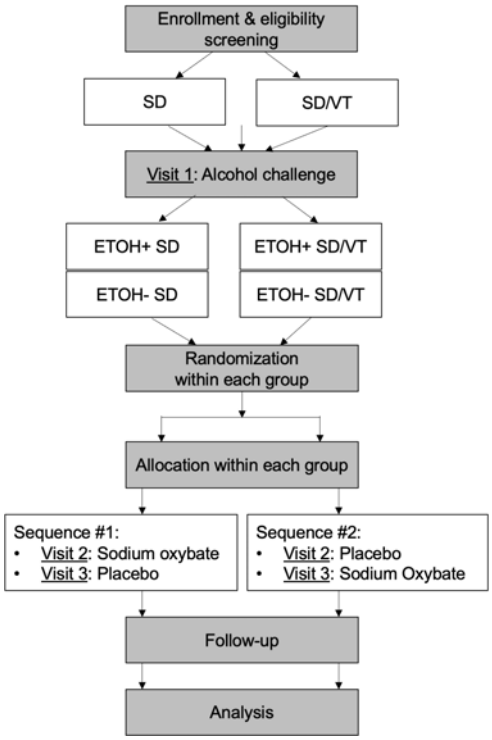

Fig. 1. Flowchart of study procedures. ETOH+ alcohol-responsive; ETOH- alcohol-non-responsive.

These evaluations will be repeated after alcohol/drug/placebo administrations, as described below. In addition, a questionnaire on side effects will be completed after administration of alcohol and treatments.

Voice and Speech Symptoms will be assessed using the patient's self-evaluation questionnaire and audio recordings of voice and speech samples. Patients will be asked to produce various vocal tasks eliciting their symptoms, 20 sentences with high vowel content to elicit ADSD symptoms, 20 sentences with high content of voiceless consonants to elicit ABSD symptoms, and to tell a narrative story. Voice and speech samples will be audio recorded immediately before and after alcohol/sodium oxybate/placebo administrations based on a schedule defined below. Audio recordings will be de-identified, randomized and blindly rated to count the voice breaks as well as to quantify harshness, breathiness, tremor, and hoarseness using a visual analog scale with three gradation indicators along a 100-mm line (normal, modulates voice, offsets voice), with distance in mm denoting the degree of deviancy from normal, as described earlier (Kirke et al., 2016).

Alcohol Challenge Test. To determine the reliability and reproducibility of patients' self-reported benefits from alcohol on voice symptom, all patients will undergo the standardized alcohol challenge test for movement disorders (Knudsen et al., 2011; Haubenberger et al., 2013; Voller et al., 2014). Oral ethanol (40%, by volume) will be administered at a total dose of 0.8 g/L of the calculated total body water. It may be mixed into 50 ml of a sugarless, uncaffeinated drink, such as diet Sprite (Watson, 1989). The same dose of alcohol will be administered for the second time 30 min after the first administration. EPIC will be used for alcohol dispensing to ensure accurate and complete documentation. The alcoholic drink will be supplied by the MEEI Research Pharmacy. The test will be performed within fixed hours between 10am-12pm. The patients will be asked to drink their

predetermined amount of alcohol as fast as possible within 5-10 min. The levels of alcohol will be assessed using breath alcohol content (brAC) readings of the breathalyzer at eight time points, including twice before the alcohol challenge and at 15, 30, 45, 60, 120 min after alcohol intake (Haubenberger et al., 2013; Voller et al., 2014). Audio recording of voice and speech samples will be synchronized with brAC measurements and rated as described above.

Randomization and Allocation. Following the alcohol challenge, patients will be randomized for the double-blind, placebo-controlled, cross-over study. The randomization will be performed by the MEEI Research Pharmacy and will be blinded for the investigators and patients. The study will be conducted under the existing Investigational New Drug (IND) application granted to the PI by the US Food and Drug Administration (FDA) for the use of sodium oxybate in SD and SD/VT patients (#117,954). Patients will be allocated 1:1 to a treatment sequence #1 of sodium oxybate/placebo or sequence #2 of placebo/sodium oxybate. Jazz Pharmaceuticals, Inc., will provide sodium oxybate and the matching placebo for research purposes, which will be sent directly to the MEEI Research Pharmacy. The placebo will be a clear solution with salty taste that matches the appearance and taste of the drug. Sodium oxybate (1.5 g = 3 ml of oral solution diluted in 47 ml of water) and the placebo (50 ml) will be formulated in sequentially numbered containers by the research pharmacy in the morning of administration. Both patients and investigators will be blinded until all outcome data are processed and the database is locked at the end of the study. EPIC will be used for study drug dispensing to ensure accurate and complete documentation.

Study drug will be administered by a licensed physician associated with this protocol.

As stated above under the *General Study Procedures* section, all patients will be assessed for their vital signs, MoCA, C-SSRS, side effects, and sleepiness immediately before and 45, 180, 300 min after drug/placebo intake. As a primary outcome measure, voice and speech recordings will be performed at the same time points. Data will be de-identified, randomized, and blindly rated for symptom severity, as described above. Our prior studies have shown that the effects of sodium oxybate (1-1.5 g) in ETOH+ movement disorders are obvious 30-45 min following drug intake and last approximately 3.5-4 hours (Frucht et al., 2005a; Frucht et al., 2005b; Arpesella et al., 2009; Simonyan and Frucht, 2013; Rumbach et al., 2016).

At discharge, patients will need to be stable and within 10% of their baseline assessment at the end of their fifth hour of monitoring. A licensed physician on the research team will evaluate and monitor patients who do not meet one or more criteria for discharge or have serious adverse events. If needed, the patient will be referred to the emergency department for a clinical care. No patient will be discharged without meeting the discharge criteria.

Patients will be required to confirm that they will not engage in important decision-making, financial and legal obligations for at least 12 hours after study participation. Patients with serious adverse events will be evaluated and referred to the emergency department for clinical care and/or admitted to hospital under Dr. Song's supervision.

Follow-up. We will follow up by phone, email or in-person with each patient after the study visits to assure that he/she has not developed any adverse side effects, in which case the patient may be asked to return to MEEI for additional evaluation. All patients will be given the contact information of the PI in order to report side effects/adverse reaction at any time.

b) 9b. Describe any data and/or sample banking, if applicable.

Response**:** Research data will be stored on the password-secured servers and password-secured image processing workstations located in the PI's laboratory. Hard copies of the results of the medical

history will be kept in the locked file cabinets located in the PI's laboratory. Only the research team will have access to the research data. Subject's identifying information will be removed and a unique research codes will be assigned for confidentiality purposes prior to data analysis. The list linking the code to the subject will be stored on the PI's password-secured server. All servers and workstations will be maintained by the Partners/MEEI IT. A database will be created, and this information/data will be encrypted using one of the software packages recommended in the MEEI IT and stored on a password-protected server with access limited to the PI and members of the research team.

c) 9c. If the study includes randomization describe the randomization process and randomization ratio, (include block size, permutations and stratification, if applicable.).

Response**:** Randomization will be performed by the MEEI Research Pharmacy as described in 9a.

d) If there are circumstances under which the researcher may withdraw participants, describe the conditions and process for withdrawal. Describe how subjects can withdraw from the study (e.g., calling or emailing the investigator/study coordinator).

Response**:** Subjects may stop taking part in this research study at any time without any penalty. This will not affect their ability to receive medical care at Partners/MEEI or to receive any benefits to which they are otherwise entitled.

Subjects may also withdraw their permission for the use and disclosure of any of their protected information for research, but they must do so in writing to the Principal Investigator.

Withdrawal without the subject's consent: The PI, the sponsor or the institution may stop subjects' involvement in this research study at any time without their consent. This may be because the research study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in their best interest, or for any other reason. If specimens or data have been stored as part of the research study, they too can be destroyed without their consent.

The subject's participation in this study may be ended if he/she fails the screening procedure or if we detect brain abnormalities in her/his MRI, such as lesions after stroke and tumor. In that case, the subject will be informed and referred to a neurologist for further evaluation.

If subject screens positively as having active suicidal ideations based the Columbia-Suicide Severity Rating Scale (i.e., and answer of "Yes" to Question 4 or 5) or spontaneously expresses suicidality, the subject will undergo an emergent evaluation by a licensed clinical member of study staff for appropriate assessment and triage. As applicable, that triage may include escorting the subject to the Emergency Department for further evaluation.

10. STUDY OUTCOMES

a) **Primary Outcome Measure(s)** - describe how you will measure the primary and other outcomes of the study (e.g., blood pressure change, changes in visual acuity using a specific test, pain scales, responses on a questionnaire, etc.). Upload copies of your data collection tools and/or a list of all variables/data points you will collect.

Note: Primary outcome measures may be measured in various ways such as:

- binary (e.g. improvement in symptoms vs. no improvement in symptoms)
- continuous (e.g. weight - kg, blood loss - mL)
- ordinal (e.g. pain - mild, moderate, severe)
- time to event (e.g. survival)
- counts (e.g. number of infections, number of events occurring)

Response**:** Primary outcome measures will include clinical improvement of voice symptoms.

b) Describe any secondary or other outcomes (exploratory): N/A

11. HYPOTHESES

Hypotheses are more specific than specific aims and are tested using predetermined statistical methods and form the basis for statistical power calculations. The primary hypothesis is a statement of the effect of the research intervention/interaction on the primary outcome measure. Hypotheses are generally stated as the null and alternative hypotheses (H0, Ha) as they have their basis in inferential statistics. Rejecting the null hypothesis with a specific level of probability indicates that there is a relationship between the variables being studied. State the alternative hypothesis which you expect your data to support.

Examples of null and alternative hypotheses

- H0: Chronic sinusitis prevalence rates are not different among children from low and high socioeconomic groups
- Ha: Chronic sinusitis prevalence rates are different among children from low and high socioeconomic groups.

a) Describe the primary hypothesis:

Response: H0: Similar to alcohol and placebo, sodium oxybate is not effective in reducing LD symptoms in EtOH+ patients but not EtOH- patients.

Ha: Similar to alcohol and in contrast to placebo, sodium oxybate is effective in reducing LD symptoms in EtOH+ patients but not EtOH- patients.

b) Describe any secondary hypotheses.

12. STATISTICAL METHODS

Describe the planned statistical methods including specific tests (e.g., parametric and non-parametric tests, estimation of incidence and prevalence rates, odds ratios, survival/failure analyses, intent to treat analyses). Provide the power calculations used to estimate the proposed sample size. If needed, please consult a biostatistician. (Note: Biostatistical consults are available through Harvard Catalyst.)

Response:
Audio recordings will be de-identified, randomized and blindly rated to count the voice breaks as well as to quantify harshness, breathiness, tremor, and hoarseness using a visual analog scale with three gradation indicators along a 100-mm line (normal, modulates voice, offsets voice), with distance in mm denoting the degree of deviancy from normal, as described earlier (Kirke et al., 2016).
Alcohol Challenge Test. All individual measures before and after alcohol intake will be compared using the equation ((Baseline-Alcohol Challenge)/Baseline) × 100%. To account for potential subjective bias and ensure reliable alcohol effects on voice symptoms, we will consider patients with ≥ 10% change of their symptoms from baseline as responsive to alcohol (ETOH+) (Haubenberger et al., 2013; Voller et al., 2014). As a secondary outcome, we will compute Pearson's correlations between symptom scores and brAC measures to examine the baseline and each time point in respect to alcohol content at a corrected $p \leq 0.05$.

Analysis. The primary outcome within each group will be examined using a linear mixed effect model with treatment (sodium oxybate and placebo) and treatment visits as interacting fixed effects and a per subject random effect at overall $p \leq 0.01$ to correct for multiple comparisons. If the interaction between the fixed effects is significant, the difference between treatments will be tested using linear contrasts of least-squares means for the fitted model at $p \leq 0.05$ adjusted for multiple comparisons. As a secondary analysis, benefit ratio will be calculated as (sodium oxybate effect – placebo effect) and analyzed using a Friedman test at $p \leq 0.01$.

13. RISKS AND DISCOMFORTS AND MINIMIZATION OF RISKS

Risk *is the probability and magnitude of harm or discomfort anticipated as a result of participation in the research.*
Minimal risk *means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*

a) Describe any risks of harm to subjects and/or anticipated discomfort(s) that are reasonably foreseeable, even if unlikely. Identify the safeguards you will put in place to minimize the occurrence of these risks and discomforts. Risks of harm and discomfort may include: physical harm/discomfort, psychological harm/discomfort, legal harm/discomfort, social harm/discomfort and economic harm.

Response**:** The daytime oral administration of sodium oxybate may entail the risks of developing dizziness, headache, somnolence, emotionality, and nausea as reported earlier (Frucht et al., 2005a; Frucht et al., 2005b; Arpesella et al., 2009). These side effects, however, have marked individual variability, are dose-dependent, observed within 10 minutes of the drug intake, and typically resolve within 30-40 minutes of dosing. Of these factors, dose is the most critical determinant of side effects. Our clinical experience with administering sodium oxybate in SD and VT patients suggests that the vast majority of these patients tolerate the 1.5 g dose without any side effects, and that, if they do develop side effects, these are extremely short lived.

There is a risk of intoxication from the alcohol that you will be given to drink. Symptoms of intoxication may include a feeling of drunkenness, slurred speech, lack of coordination and concentration, nausea, flushing of your face, or feeling hot.

There may be remote risk of loss of data. We will make every attempt to prevent the privacy and confidentiality risk by replacing personal identifying information with codes and by keeping encrypted digital data on the password-secured computer.

b) If applicable, describe any group harms (i.e. research that focuses on a specific group or population that if the results are disclosed, could harm the group as a whole).

Response**:** N/A

c) Describe any anticipated circumstances in which a "breach of confidentiality" associated with a mandated disclosure (e.g. reporting abuse to authorities) may occur as part of this study?

Response**:** N/A

d) What risk classification (taking into consideration the probability and magnitude of harm) is appropriate for the proposed research?

□ Minimal Risk X□Greater than Minimal Risk □ Unknown

e) Explain why you feel this category is appropriate based on the definition above (if more than minimal risk, describe the likelihood and seriousness of such risks).

Response**:** The participants will receive, on separate visits, alcohol and sodium oxybate, which is a Schedule III controlled substance. Therefore, the risk is classified as Greater than Minimal Risk. However, the risk of serious adverse events is very low given the low dose of administered sodium oxybate and alcohol.

14. ALTERNATIVES

Describe any alternatives, to research participation available to potential patients.

Note: If there are no alternatives, other than "not participate" state so.

Response**:** The alternative is not to participate in the study.

15. BENEFITS

a) Will individual subjects have any direct benefits from the research? If subjects will not experience direct benefit, state so.

Response**:** It is possible that patients might benefit from participation in this trial, if sodium oxybate is developed as a symptomatic treatment for SD and VT.

b) Explain the potential benefits to science, and/or society as a result of this research.

Response: Possible benefits from participation in this study include learning whether or not sodium oxybate might help improve symptoms of SD and VT.

c) If this study is more than minimal risk, explain how the risks are minimized in relation to the anticipated benefits of the study:

Response**:** N/A

16. DISSEMINATION OF RESULTS

a) Describe any plans to share research results with subjects, EITHER individual results and/or aggregate results. If there are no plans to share results, explain why this is not feasible, appropriate, or applicable to this research.

Response: The results of the studies will be shared with the subjects upon the publication of the findings. At that time, the subjects who participated in each research study will receive a letter in lay language explaining the details of findings as published in a peer-reviewed journal.

b) How will results be published, and in what form (newsletter to subjects, peer-reviewed publications)?

Response: The results of the studies will be shared with the subjects upon the publication of the findings. At that time, the subjects who participated in each research study will receive a letter in lay language explaining the details of findings as published in a peer-reviewed journal.

17. INCIDENTAL FINDINGS

If there is the possibility that study procedures may identify incidental findings of medical importance to a subject and/or the subject's family (e.g., genetic studies, imaging studies, studies that conduct routine blood tests, etc.), describe the plan for reporting any incidental findings (e.g., study physician will discuss with subject/subject's PCP, genetic counseling). In addition, researchers may uncover evidence of child, domestic, or elder abuse, which require reporting to authorities. Please describe the plan for reporting such findings.

Response: In case of incidental findings of clinical relevance, the patient or his/her referring physician will be notified for a follow up.

18. PRIVACY/CONFIDENTIALITY

NOTE: MEE researchers must adhere to MEE Information Security Policies and Procedures when designing their research protocols. The HSC evaluates the collection, use and storage of data and may require additional safeguards. For example, the HSC may require a Certificate of Confidentiality for research projects that collect personally identifiable, sensitive information.

a) Describe the plan for protecting the privacy and confidentiality of subjects throughout the research (e.g., limited access to medical records and identifiable study data, data security procedures consistent with MEE Information Security Policy).

Response: Every effort will be made to respect and maintain the confidentiality of study participants according to current legal requirements and as required by the Federal Privacy Act.
All communications with the subject, such as consent, screening, phone messages, mail, etc., and study related information shared by a patient will be kept strictly private at all times. Consenting and screening of patients will be done in a private room, with only research members present. Subjects will be informed that they may choose not to answer a specific question about their medical history, however, this may present one of the reasons for exclusion as determined by a research team. Data security procedures will be consistent with MEEI Information Security Policy.
Confidentiality with respect to names, medical, treatment and family information, examination findings, and laboratory findings will be maintained. The patient's name is present in the patient medical record. When extracting data from the patient medical record for research purposes, the information may contain identifiers for the purpose of linking the extracted information back to additional data in the source document.
In the event that clinical information (including examination findings, laboratory findings, family history, medical and treatment information) or data derived from this information is presented at scientific meetings, for teaching, or for publication, the subject's name or the family name will not be disclosed. In the event that videotapes, audiotapes, and/or photographs are used at scientific meetings, for teaching, or for publication, the subject's name or the family name will not be disclosed, but the subject's face may be visible.

b) Where will you store research data, signed informed consent forms, and assent forms to maximally protect privacy and confidentiality?

Response: All research data will be stored on password-protected and secured network attached servers in the PI's laboratory. Medical information and questionnaires will be stored in the locked file cabinets in the PI's laboratory.

c) Please provide the plan for destroying identifiers (at the earliest opportunity as consistent with the research plan) or provide a health or research justification for retaining identifiers. For protocols subject to future and secondary data analysis, provide justification for not destroying identifiers permanently and explain plans for future use (i.e., establishment of a data or specimen repository).

Response: Scans and blood samples will originally have the identifiers, which will be removed before the data analysis will be conducted. All scans and blood samples will receive a unique research code when the subject identifiers are removed. The list linking the code to the subject will be stored on the PI's password-secured server. All research data will receive a unique research code when the subject identifiers are removed. All video and audio files will be removed from the recording device immediately after the recording and transferred to the secured, encrypted server. All video and audio files will be de-identified before data analysis.

d) Will you obtain samples/data from outside sources? Please specify from whom you will obtain samples and what information you will obtain with each sample. Please note that a Material Transfer Agreement may be required for this research activity. (Contact Research Administration for instructions.)

Response: N/A

e) Will samples from MEE be provided to outside sources? Please specify to whom you will provide MEE samples and what information/data will accompany each sample. Please note that that a Material Transfer Agreement will be required for this research activity.

Response: De-identified voice and speech recordings will be shared with Dr. Anna Rumbach at the University of Queensland via Partners Dropbox Business account. Dr. Rumbach will be fully blinded to the identity of participants and to their time points of participation in this study. She will be involved in the analysis of these data according to the data analysis protocol described above.

19. DATA and SAFETY MONITORING PLAN (DSMP)

a) If the research is no more than minimal risk, describe any provisions in place to ensure the safety of participants. In minimal risk studies, there is always the risk of loss of confidentiality and privacy. However, minimal risk studies involving blood draws, imaging, and eye exams may have risks associated with the study procedure.

Response**:** Please see response under 13a.

b) If the research is <u>more than minimal risk,</u> please provide a detailed data and safety monitoring plan (DSMP). Include the individual(s) or group responsible for data and safety monitoring (e.g., PI, specific members of the study team, independent monitor(s), a convened Data and Safety Monitoring Board - DSMB). Please see the guidance document in IRBNet for developing a DSMP.

Response**:**
Detailed Monitoring Plan, Data Management and Quality Assurance Plan, and DSMB Charter are enclosed as separate documents.
Because of a drug administration, the DSMP will be followed. The PI will be responsible for internal data review to verify adherence to the protocol, local regulations on the conduct of clinical research,

and ensure completeness, accuracy, and consistency of the data. Ms. Alexis Worthley will serve as an external monitor and will perform external monitoring, including the rates of recruitment, ineligibility, noncompliance, protocol violations and dropouts; completeness and timeliness of the data; accrual within important subsets according to the Monitoring Plan. Dr. David Jung and Dr. Glen Bunting will serve as members of the Data and Safety Monitoring Board and will be responsible for the review of safety and efficacy of data and the assessment of the risk to the research subject‘s health and well-being according to the DSMB Charter. Specific items for monitoring will include the integrity of research records in compliance with institutional policies, adverse events, subject compliance with the protocol, and subject drop-out. The External Monitor and DSMB will be responsible for providing recommendations for the study continuation, amendment, or discontinuation.
Internal monitoring by the PI will be conducted on a monthly basis or as frequent as needed; external monitoring by Ms. Worthley will be conducted after the enrollment of each 10 subject; DSMB monitoring will be performed on a bi-annual basis.
Adverse effects will be recorded in the research chart and adverse events log and reported to the MGB IRB in accordance with Federal policies and as described in the institutional policy on Unanticipated Problems Involving Risks to Subjects or Others. The NCI CTC (Common Toxicity Criteria) will be used to evaluate adverse events. Research charts will be reviewed for all recorded information about the research procedures completed and documented adverse events.
The study will be terminated when an adequate amount of data is collected. If a serious unexpected adverse event occurs that might indicate undue risk and could not be prevented for future participants, then the study would be stopped.

Please see enclosed the detailed DSMP.

c) Provide information related to the expertise and qualifications of the individual(s) and/or groups listed above relative to monitoring.

Response: Dr. Simonyan has research and clinical expertise in SD and VT and has conducted the open-label study of sodium oxybate in these disorders according to a very similar research protocol. Dr. Bunting is an expert speech-language pathologist who has a long-standing interest in SD and VT research. Dr. Jung is an otolaryngologist who has special interests in the development of novel methods for cochlear drug delivery and understanding mechanisms of noise- and age-related hearing loss. Ms. Worthley is a Clinical Research Coordinator II at the MGH Department of Psychiatry, Division of Neuropsychiatry and Neuromodulation. She has relevant experience and training in the conduct of human research and is familial with this protocol and procedures.

d) Please explain how data and safety monitoring activities for this study will be documented (e.g., a monitoring log kept in the regulatory binder).

Response**:** All research procedures and research documentation will be reviewed by the PI and her research team on a monthly basis or as frequent as needed for their completeness, accuracy, validity and integrity of the data in adherence to the IRB-approved protocol according to the Data Management and Quality Assurance Plan. The External Monitor (after each 10 subjects are recruited) and DSMB (bi-annually) will help the PI maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study according to the procedures described in the Monitoring

Plan and DSMB Charter. During this three-tiered review, the informed consent, subject recruitment and follow-up, study allocation, subject compliance with the study procedures, Adverse Event documentation and reporting, and quality of data will be monitored.

e) Explain if any individual involved in monitoring has relationships with sponsors, organizers or researchers, conducting the study, and if applicable, describe the nature of these relationships.

Response: No relationship with sponsors or organizers. The statement of conflict of interest from the external monitor and DSMB members will be obtained prior to each monitoring meeting.

f) If applicable, describe the process for communication of Data and Safety Monitoring Board reports to the investigator and to the HSC.

Response: Following each DSMB meeting, a written report will be generated that will include the findings and recommendations of the DSMB. The report will be sent to the PI and, in case of serious adverse events and/or protocol deviations, to the MGB IRB. See details in the Data and Safety Monitoring Board Charter.

20. DATA REVIEW AND QUALITY ASSURANCE

a) Specify the frequency of data review (a specific number of times, at defined time points, after enrollment of a certain number of subjects, or as needed).

Response**:** All research procedures and research documentation will be reviewed by the PI and her research team on a monthly basis or as frequent as needed for their completeness, accuracy, validity and integrity of the data in adherence to the IRB-approved protocol according to the Data Management and Quality Assurance Plan. The External Monitor (after each 10 subjects are recruited) and DSMB (bi-annually) will help the PI maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study according to the procedures described in the Monitoring Plan and DSMB Charter.

b) Who will be responsible for data review (e.g., PI, study staff)? If data review is shared, describe each person(s) or group responsibility.

Response**:** PI will be responsible for data review.

c) If applicable, please describe the electronic data capture systems you will use and describe the training provided for those who will use these systems.

Response**:** Voice and speech recordings and all other electronic records will be stored on the institutional, password-protected network attached server folders dedicated to this protocol that are maintained by the MGB IT and are an exempt from ELN. These research data are accessible only to the research staff named on this protocol. All research staff has been trained by the PI and MGB/MEE Research IT on the use of network attached server.

d) What processes are in place for addressing unresolved or significant issues (e.g., significant noncompliance with the protocol) identified by data review at MEE (or across study sites, when applicable)?

Response: All data will be reviewed on ongoing bases, at least once monthly, to avoid noncompliance with the protocol. In addition, all experimental procedures will be reviewed and documented on regular bases or as needed to avoid protocol deviations or violations. See details in the Monitoring Plan and the Data Management and Quality Assurance Plan.

21. ADVERSE EVENTS

a) Describe how and by whom adverse events will be identified.

Response**:** Adverse events will be identified and recorded by the research team and/or as reported by a participant.

b) Describe any "drop criteria" for individual research subjects who experience an adverse event including who will be responsible for making these determinations.

Response**:** In unlikely case of serious adverse events, the PI will be responsible for exclusion of subjects due to an adverse event.

c) Describe any "stopping rules" for parts of the study, or for the entire study due to adverse events including who will be responsible for making these determinations.

Response**:** If a serious unexpected adverse event occurs that might indicate undue risk and could not be prevented for future participants then the study would be stopped.

d) Please acknowledge and state that adverse events and unanticipated problems will be reported to the HSC in accordance with the HSC policy on Reporting Adverse Events and Unanticipated Problems.

Response**:** The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with IRB requirements and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the IRB. All unanticipated and adverse events, both serious and non-serious that result in the subject's withdrawal from the study, will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines within 5 working days/ 7 calendar days of the date the investigator first becomes aware of the problem. All other unanticipated incidents, experiences, information, outcomes, or other problems that indicate that the research places subjects at an increased risk of physical, psychological, economic, legal, or social harm than was previously known or

recognized will be submitted through Insight/eIRB as an Other Event. All adverse events, deviations, and unanticipated problems will be summarized and reported at the time of Continuing Review.

Title: Sodium oxybate in spasmodic dysphonia and voice tremor
PI Name: Simonyan, Kristina
Sponsor Name: NIH-NIDCD National Institute on Deafness and Other Communication Disorders
Protocol #: 2019P001680

Major Modifications

Type: Amendment (AME11)
Date Received: March 08, 2021
Date Approved: March 18, 2021

Requested changes and rationale: The enrollment of the human subjects and the conduct of the study procedures under this protocol have been significantly impacted by the pandemic-related research lockdown in March 2020. The study was reopened for recruitment in December 2020, following a 10-month delay.
This study is an NIH-funded clinical trial. Given the delays due to the pandemic, the study will not be completed within the timelines as planned and proposed in the NIH grant. The PI discussed this delayed timeline and recruitment with the DSMB (see below) as well as the NIH/NIDCD Program Office. To facilitate the study completion while minimizing further delays, the DSMB recommended adjusting the human subject recruitment so that the enrollment is focused on patients with alcohol-positive and alcohol-negative spasmodic dysphonia (SD, also known as laryngeal dystonia (LD)) and dystonic voice tremor (VT or DTv). These patients contribute to 2 experimental groups, and their accrual is relatively satisfactory. It was recommended by the DSMB to remove the additional group of patients with vocal fold pathology who served as the third negative control group. It is expected that this adjustment to the human subject recruitment will speed up the enrollment of the main experimental groups and will not impact the overall outcomes of this study.
This amendment is a request to adjust the human subject recruitment according to the DSMB recommendation and discussions with the NIH Program Officer. There are no changes to the protocol procedures. The protocol, consent and relevant forms and documents are updated to remove the vocal fold nodule group. There is no change in risks and benefits to the subjects. The adjustment to the human subject recruitment will be reported to the NIH at the time of the annual progress report. This change will also be reported to the FDA at the time of the annual progress report. The CT.gov record will be updated accordingly.

DSMB Report Summary (Date: 02/11/2021)
Data safety and monitoring procedures were reviewed on February 1, 2021.
The study procedures were significantly impacted by the COVID-19 pandemic. No subject was recruited between 3/9/2020 and 12/13/2020 due to the mandatory full or partial research shutdown and due to the restrictions of the study procedures requiring unmasked subjects to perform multiple speech recordings.
The study was re-opened with the strict safety measures in place in December 2020. Two subjects were consented between 12/14/2020 and 02/08/2021. All procedures for recruited subjects were performed as planned. No major deviations were identified. One minor deviation related to the study-unrelated technical issues with the MRI scanner was identified. Mild side effects in both subjects were documented and discussed. No severe adverse events were identified. The recruitment is expected to remain slower than usual due to the ongoing pandemic.
The DSMB reviewed the study design and procedures with respect to the overall recruitment and the reasonably timely completion of the study. The current study design includes the

experimental patient group of ETOH-positive spasmodic dysphonia (SD) and spasmodic dysphonia/voice tremor (SD/NT) and the control patient group of ETOH-negative SD, SD/VT and vocal fold nodules (VFN).
It was discussed that the data from the control group of VFN patients will provide only ancillary information about the benefits and neural mechanisms of action of sodium oxybate, this information will not be relevant to sodium oxybate's effects in SD and SD/VT, and that this information will not have a direct impact on statistical analysis or the primary outcome of this study.
Given the ongoing, pandemic-related challenges with the recruitment of human subjects and the conduct of clinical research studies, the DSMB recommended to adjust the subject recruitment by removing the VFN patient group from the study design. The experimental and control groups of ETOH-positive and ETOH- negative SD and SD/VT patients will continue as planned.
The DSMB-recommended protocol modification to remove the VFN patient group will be submitted to the MGB IRB. The notification of a change in human subjects will be communicated to the NIH/NIDCD, FDA, and Jazz Pharmaceuticals.

Type: Amendment (AME17)
Date Received: December 21, 2021
Date Approved: December 27, 2021

Requested changes and rationale: Because of the rapidly increasing rate of Covid-19 infection and because patients under this protocol travel from the different US states for study participation and conduct study procedures, including speaking, shouting, and singing, fully unmasked, we are requesting to add a Covid-19 screening test prior to study participation, if applicable.
In case the test is positive, the current clinical procedures will be followed by the licensed clinician on the protocol.
The Summary Protocol and Detailed Protocol have been updated accordingly. The screening form has been added in the Attachments and will be used as applicable. There are no changes to the consent form because this is a pre-study screening.

Protocol Title: Central Mechanisms and Treatment Response of Sodium Oxybate in Spasmodic Dysphonia and Voice Tremor

Principal Investigator: Kristina Simonyan, MD, PhD, Dr med

Site Principal Investigator:

Description of Subject Population: Patients with spasmodic dysphonia, voice tremor

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Key Information

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. Your decision won't change the medical care you get within Partners now or in the future.

The following key information is to help you decide whether or not to take part in this research study. We have included more details about the research in the Detailed Information section that follows the key information.

Why is this research study being done?

The purpose of this study is to learn how a new oral drug, sodium oxybate (Xyrem®), improves symptoms of spasmodic dysphonia (SD) and voice tremor (VT). SD and VT are neurological conditions that cause uncontrollable spasms and shaking of the vocal cords and impair voice and speech production. Some people who will take part in this study do not have SD or VT, affecting voice production.

How long will you take part in this research study?

Your participation in this research study is expected to include up to 4 separate visits. If you decide to join this research study, your participation will include a screening examination, voice and speech recording, a blood sample draw, magnetic resonance imaging (MRI) of your brain, alcohol test, and drug and placebo intake.

What will happen if you take part in this research study?

If you take part in this study, we will give you alcohol, sodium oxybate, and placebo (each on a separate day) to look at their effects on SD and VT symptoms. We will then use brain imaging to see how these treatments affect the brain in people whose voice symptoms improve and do not improve with treatment. Sodium oxybate is FDA approved for the treatment of excessive daytime sleepiness associated with narcolepsy. The use of sodium oxybate in this study is investigational because it is not approved for treatment of SD or VT. This means that it can only be used in research studies in people with SD or VT.

Other study procedures include: screening tests, voice and speech recording, blood draw, brain MRI, alcohol, drug and placebo intake.

Why might you choose to take part in this study?

You will not benefit from taking part in this research study. Others with dystonia may benefit in the future from what we learn in this study. However, voice symptoms in SD and VT patients may be better for a few hours after taking alcohol and/or the study treatment. Information gained from this study will help us learn more about SD and VT, which may lead to better treatments in the future.

Why might you choose NOT to take part in this study?

Taking part in this research study has some risks and requirements that you should consider carefully.

Important risks and possible discomforts to know about include possible discomforts from being in the MRI scanner, the blood draw, alcohol and drug intake.

People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips, metallic prostheses, permanent eyeliner, implanted delivery pump, or shrapnel fragments. People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. It is not known if MRI is completely safe for a developing fetus. Therefore, the scan will not be done if the pregnancy test is positive. There are no known long-term risks of MRI scans.

The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw. There is a risk of adverse social or economic outcomes associated with the inadvertent release of genetic information. Some people have been discriminated against because of genetic disorders.

The daytime intake of sodium oxybate may entail the risks of developing dizziness, headache, somnolence, emotionality, and nausea. These side effects, however, have marked individual variability, are dose-dependent, observed within 10 minutes of the drug intake, and typically resolve within 30-40 minutes of dosing. Of these factors, dose is the most critical determinant of side effects.

Symptoms of intoxication from alcohol may include a feeling of drunkenness, slurred speech, lack of coordination and concentration, nausea, flushing of your face, or feeling hot.

There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk.

A detailed description of side effects, risks, and possible discomforts can be found later in this consent form in the section called “What are the risks and possible discomforts from being in this research study?”

Other things to consider are travel requirements for study participation.

If you have questions or concerns about this research study, whom can you call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Dr. Kristina Simonyan, MD, PhD, Dr med, is the person in charge of this research study. You can call her at 617-573-6025 during regular business hours. You can also call Azadeh Hamzehei Sichani, MA, at 617-573-6016 during regular business hours with questions about this research study.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research
- Any pressure to take part in, or to continue in the research study

Detailed Information

A description of this clinical trial is available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site does not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Why is this research study being done?

We are doing this research to learn how a new oral drug, sodium oxybate (Xyrem®), improves symptoms of spasmodic dysphonia (SD) and voice tremor (VT). Some people who will take part in this study do not have SD or VT. SD and VT are neurological conditions that cause uncontrollable spasms and shaking of the vocal cords and impair voice and speech production. Treatment of SD and VT is limited to injections of botulinum toxin into the vocal cords, however, it is often only partially effective and can have side effects. More than half of people with SD and VT (57%) have some relief from drinking alcohol. A previous study showed some of the ways in which sodium oxybate (an oral drug that acts similar to alcohol) changes brain activity and improves symptoms of SD and VT. However, we do not fully understand the effects of this drug on voice symptoms or on brain areas that might be important in the response to sodium oxybate.

In this study, we will give the participants alcohol, sodium oxybate, and placebo (each on a separate day) to look at their effects on SD and VT symptoms. A placebo looks like the study drug but contains no active drug. We will then use brain imaging to see how these treatments affect the brain in people whose voice symptoms improve and do not improve with treatment.

Sodium oxybate is FDA-approved for the treatment of excessive daytime sleepiness associated with narcolepsy. The use of sodium oxybate in this study is investigational because it is not approved for treatment of SD or VT. This means that it can only be used in research studies in people with SD or VT.

Who will take part in this research?

There will be four groups of patients in this study:

1. Patients with SD whose voice symptoms improve with alcohol
2. Patients with SD whose voice symptoms do not improve with alcohol
3. Patients with SD and VT whose voice symptoms improve with alcohol
4. Patients with SD and VT whose voice symptoms do not improve with alcohol

Each group will have up to 35 participants. A total of about 140 patients will take part in this research study. In addition, brain imaging data in 35 healthy subjects will be used from our existing database for comparisons with patients' data. Healthy subjects will not be given the study treatments.

National Institute on Deafness and Other Communication Disorders, National Institutes of Health is paying for this research to be done. The study drug, sodium oxybate, is being provided by Jazz Pharmaceuticals.

What will happen in this research study?

Your participation in this research study is expected to include up to 4 separate visits. If you agree to participate in this research study, the following information describes what may be involved.

Visit 1: Screening Assessments and Baseline MRI
During this visit, we will do some tests to figure out whether you are eligible for the study. This visit is expected to last up to 3 hours.

The following procedures will be performed:

- **Intake Questionnaire and Screening:** During this visit, we will explain the study to you. We will ask you about your past and present medical problems and measure your vital signs, including height, weight, heart rate and blood pressure. We will ask you to answer some questions and complete some questionnaires.
- **Urine pregnancy test:** If you are a woman of childbearing potential, we will ask you to provide a urine sample for a pregnancy test within 24 hours before the MRI scan. If you are pregnant you cannot take part in the study.
- **Voice and Speech Recording:** We will digitally record and videotape your voice and speech while you while you repeat some sentences and sounds. The entire recording will last about 15 minutes. Your voice and video recordings will be kept after the study is complete so that they can be used to review the study procedures. Your name will be removed from the recordings, and a unique code will be assigned to your recordings to store them indefinitely on a password-protected computer in the PI's laboratory.

  Do you agree to let us store your samples and health information for future research related to dystonia?

  ☐ YES ☐ NO Initials____

  If later you change your mind and want your samples destroyed, contact the study doctor.

- **Blood draw or saliva collection:** We will ask you to provide a small amount of blood or saliva to find genes that may be responsible for the treatment response. We will draw about 8-15ml (up to 3 teaspoons) of blood from a vein in your arm. If you are unable to provide the blood sample, we will ask you to provide a saliva sample of about 2 ml (up to one quarter of teaspoon) by spitting into the special funnel. Your blood or saliva samples will not

be identifiable that is your name will be removed and replaced with a unique study code. Your samples will not be discarded when this research study is completed. They will be saved in a freezer located in the PI's laboratory indefinitely.

We will use your blood or saliva sample to get the DNA in your cells. Genes are made of DNA. Traits that are inherited (passed through families) are coded in your genes. We will conduct DNA analysis for research purposes only. Therefore, our research results will not have any clinical relevance to your health or the health of your family members. We will not provide the results of research DNA analysis back to you because further studies may be necessary before these results are meaningful.
We may also perform a whole genome analysis on your DNA sample. Usually researchers study just a few areas of your genetic code that are linked to a disease or condition. In whole genome analyses, all or most of your genes are looked at and used by researchers to study links to dystonia.
In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that analyze data and collect the results of whole genome studies. These banks may also analyze and store DNA samples, as well. These central banks will store your genetic information and samples and give them to other researchers to do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data will be sent with only your code number attached. Your name or other directly identifiable information will not be given to central banks. There are many safeguards in place to protect your information and samples while they are stored in repositories and used for research.

- **Baseline brain scan (functional MRI - fMRI):** MRI uses a strong magnetic field and radio waves instead of X-rays to obtain images of body organs and tissues. This technique is more sensitive than X-rays in some circumstances. There is no radiation exposure because X-rays are not used. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, we will place you on a table that can slide in and out of the cylinder. In the scanner, you will hear loud knocking noise, and you will wear earplugs to muffle the sound. You will wear headphones and a microphone to communicate with the MRI staff during your scan. We will use the MRI machine to take pictures of your brain while you are simply lying still in the scanner and while you are producing syllables and short sentences.
  We will conduct the MRI scan for research purposes only. The information we obtain from this study will not provide information on your health. You will not receive your research results. However, if we detect brain abnormalities in your MRI scan, such as lesions after stroke or tumor, we may inform you or your physician and may refer you for further evaluation.
  You may have a light meal prior to the MRI scanning.

If you are eligible to continue your participation in this study, the following describes the next three visits.

Visit 2: Standardized Alcohol Challenge Test and MRI

During this visit, we will test whether your voice symptoms improve with alcohol. You will be given about 50 ml (10 teaspoons or 1 shot) of alcohol to drink twice, with 30 min between each intake. The alcohol will be supplied by the MEEI Research Pharmacy and mixed with a non-caffeine drink, such as diet Sprite. The exact amount of alcohol you receive will be based on your weight, height, age, and gender. We would like you to drink the entire amount of alcohol you are given within 5 minutes. We will examine you to see if your voice symptoms improve with alcohol. We will ask you to produce some syllables, sentences or tell a story. We will also ask you questions about your capacity for judgment and reasoning, possible suicidal thoughts, and the level of sleepiness. We will examine your breath alcohol content by asking you to blow through a special tube with one breath. We will conduct these procedures twice before and 15, 30, 45, 60 and 120 minutes after drinking alcohol.

At 60 min after alcohol intake, when the amount of alcohol in the blood reaches its highest level, we will conduct the second MRI scan. This scan will be similar to the first baseline MRI scan that you performed during Visit 1.

This visit is expected to last up to 3 hours. Visits 1 and 2 can be combined based on your schedule, MRI scanner availability, and time allocations by the research team.

Visits 3 and 4: Drug or Placebo Treatments

During these visits, we will test whether your voice symptoms improve with sodium oxybate and the placebo. Visit 3 and Visit 4 will be scheduled on separate days. Both Visit 3 and Visit 4 may take up to six hours. You may have light meal about 2 hours before each Visit.

The following procedures will be performed during each Visit.
We will first examine your vital signs, such as blood pressure, pulse, height and weight. Your voice and speech will again be recorded and videotaped. We will also ask you several questions about your thought process, possible suicidal thoughts, and the extent of sleepiness in everyday situations.

We do not know if sodium oxybate affects pregnancy or fetal development. Therefore, sexually active women who are able to get pregnant and men who are able to father a child must agree to use a reliable method of contraception during participation in this study.

You are required to confirm that you will use reliable methods of contraception, such as continuous abstinence, barrier and hormonal methods, implantable devices, or permanent birth control methods, before and during the treatment study.

Do you agree to the above statement?

☐ YES ☐ NO Initials____

The MEEI Research Pharmacy will provide the study treatment during Visit 3 and Visit 4. The study treatment will be chosen by chance, like flipping a coin, by the MEEI Research Pharmacy. Neither you nor the research team will choose or know what study treatment you get. However, this information can be obtained in an emergency. During each visit, you will be given clear liquid (about 50 ml) that will contain either the drug (sodium oxybate) or the placebo. On one of these visits, you will receive a single dose of 1.5 g of sodium oxybate, which will be diluted in clear water (about 50 ml). On the other visit, you will receive the placebo, which will be clear liquid (about 50 ml) with the salty taste similar to that of sodium oxybate. We would like you to drink the entire amount of liquid you are given within 5 minutes.

About 45 minutes after you receive the treatment, we will ask you to produce syllables, sentences and tell us a story, which we will digitally record and videotape to examine your voice symptoms. We will record your vital signs and ask you questions about your judgment, reasoning, and possible suicidal thoughts. We will also ask you if you feel sleepy, drowsy, dizzy, or have nausea. These assessments will be repeated at 3 hours after the treatment.

About 60 minutes after each treatment, we will conduct a brain MRI scan. These scans will be similar to the MRI scans you performed during Visit 1 and Visit 2.

Discharge

You will remain under the observation of the research team during the entire study visits. At the end of study procedures during each visit, we will confirm that your vital signs are within the normal range and that you do not experience any side effects because of alcohol intake or study treatments. We will also examine your thought process, the level of sleepiness, and possible suicidal thoughts.

You will be discharged 5 hours after the intake of study treatment if your vital signs are stable, you walk independently, have steady gait without dizziness, nausea, vomiting, have no pain, no sleepiness, are cognitively alert and oriented to time, place and person. If you have an accompanying person, you may leave earlier (usually about 3.5 hours after the study treatment) when all study procedures are completed.

If you do not meet these discharge criteria, you will remain under the observation of the research team and the licensed physician until the time your vital signs are normal and/or you do not experience any side effects. In rare cases, you may be referred to an emergency department for further evaluation.

You are required to confirm that you will not engage in any important decision-making, financial and legal obligations for at least 12 hours after receiving study treatment.

Do you agree to the above statement?

☐ YES ☐ NO Initials____

You are required to confirm that you will not consume alcohol for at least 12 hours after receiving treatment. Do you agree to the above statement?

☐ YES ☐ NO Initials____

We will follow up with you by phone or email on the next day after study participation to determine whether you have developed any side effects. If so, you may be asked to return to MEEI for additional evaluation.

How may we use and share your samples and health information for other research?

The samples and information we collect in this study may help advance other research. If you join this study, we will remove all information that identifies you (for example, your name, medical record number, and date of birth) and use these de-identified samples and data in other research. It won't be possible to link the information or samples back to you. Information and/or samples may be shared with investigators at our hospitals, at other academic institutions or at for-profit, commercial entities. You will not be asked to provide additional informed consent for these uses. If you have participated in other studies conducted by your study doctors, results collected in those other studies may be used in this study if you provide permission for this use of your study data.

Do you agree to let us use your samples, results, and health information from other studies in this study?

☐ YES ☐ NO Initials____

Do you agree to let us use your samples, results, and health information from this study in other studies, including future research?

☐ YES ☐ NO Initials____

Will you get the results of this research study?

You and your doctor should not expect to get information about the results of the research study or the results of your individual participation in the research study. We will study samples and information from many people. It could take many years before anyone knows whether the results have any meaning. There is a small chance that we could find out something from the study that might be important to your health. If this happens, we may contact you to find out if you would like to learn more. However, even if we find something important to your health, we cannot guarantee that you will be contacted.

You can choose to get a newsletter from Dystonia Medical Research Foundation or National Spasmodic Dysphonia Association that will tell you about the research studies we are doing. This newsletter will not announce your results or anyone else's, but it will tell you some information about what we are learning about dystonia. We will also publish what we learn in medical journals. We may send you a letter describing information we learned about dystonia based on this study. In the future, when research results are published, they may show that certain groups (for example, racial or ethnic groups, or men/women) have genes that are associated with increased risk of a disease. If this happens, you may learn that you are at increased risk of developing a disease or condition.

Review of Medical Records from Hospital Admissions or Emergency Department Visits

Mass General Brigham (MGB) has an electronic system that lets your study doctors know if you are admitted to an MGB Hospital, or if you visit an MGB Hospital Emergency Department. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

What are the risks and possible discomforts from being in this research study?

Magnetic Resonance Imaging

MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, persons with metal implants, such as surgical clips, or pacemakers should not have an MRI. All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes

images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request. If you are or suspect you are pregnant, you should not participate in this study. The MRI has the potential, during normal routine use, to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped.

Some people experience dizziness or rarely nausea when going into an MRI scanner and these sensations may be more common in scans with higher magnetic fields. In most cases, these symptoms only last a short time. However, some people may experience them throughout the scan and/or continue to experience them for a short period of time after; generally, less than half an hour. No case of permanent problems is known.

Sodium oxybate intake

The daytime intake of sodium oxybate may entail the risks of developing dizziness, headache, somnolence, emotionality, and nausea. These side effects, however, have marked individual variability, are dose-dependent, observed within 10 minutes of the drug intake, and typically resolve within 30-40 minutes of dosing. Of these factors, dose is the most critical determinant of side effects.

Alcohol intake

Symptoms of intoxication from alcohol may include a feeling of drunkenness, slurred speech, lack of coordination and concentration, nausea, flushing of your face, or feeling hot.

Blood draw

The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw. These risks will be minimized by using skilled staff to perform the blood draws.

Genetic studies

There is a risk of adverse social or economic outcomes associated with the inadvertent release of genotyping results. Some people have been discriminated against (lost jobs, denied insurance) because of genetic disorders. Please be mindful of the purpose for which the information will be used before giving others your medical or genetic information. We will keep all such information confidential to the extent legally possible. Blood drawn for DNA samples will not be used in other research studies without obtaining your approval.
There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers, except those with fewer than 15 employees, to discriminate against you based on your genetic

information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Private information

There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk. We will make every attempt to prevent your privacy and confidentiality risk by replacing your personal identifying information with codes and by keeping encrypted digital data on the password-secured computer.

There may be other risks that are currently unknown.

What are the possible benefits from being in this research study?

It is important to know that you may not get any benefit from taking part in this research. Others may not benefit either.

Can you still get medical care within Partners if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should you do if you want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will you be paid to take part in this research study?

If you agree to take part in this research study, we will pay you $200 for your time and effort after the study completion. If you complete only a portion of the study, we will pay you $50. If you are traveling from of out of town to participate in this study, we will reimburse your travel costs, including air/train/car fare and lodging. Meals will not be reimbursed. A dated receipt should be provided for reimbursement of any travel expenses incurred.

We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples or information are used for this purpose.

What will you have to pay for if you take part in this research study?

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

What happens if you are injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the beginning of this consent form.

If you take part in this research study, how will we protect your privacy?

Federal law requires Partners to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- Partners researchers and staff involved in this study
- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study
- The Partners ethics board or an ethics board outside Partners that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within Partners who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections), state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Other researchers within or outside Partners, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate,

unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your identifiable information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with the law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

_____	_____	_____
Subject	Date	Time

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

_____	_____	_____
Study Doctor or Person Obtaining Consent	Date	Time

Consent Form Version Date: 06/01/2021