PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Official Title: **A Clinical Trial of a Hemp-Derived Cannabidiol Product for Anxiety**

Principal Investigator: **Dr. Staci A. Gruber, Ph.D.**

NCT Number: **NCT04286594**

Document Date: **05/12/2023**

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Staci A. Gruber, Ph.D.

PROTOCOL TITLE
A Clinical Trial of a Hemp-Derived Cannabidiol Product for Anxiety

FUNDING
Sponsored by Charlotte's Web (formerly known as Stanley Brothers Bio Tec)

VERSION DATE
5/12/2023

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

The proposed investigation is designed to examine the impact of 6 weeks of treatment with a sublingual high-cannabidiol industrial hemp-derived compound on individuals with symptoms of anxiety.

Specific Aim 1: To assess pre- and post-hemp treatment clinical state ratings of anxiety and quality-of-life ratings in individuals with symptoms of anxiety.

Specific Aim 2: To assess pre- and post-hemp treatment performance on a range of neurocognitive measures designed to examine cognitive function.

Specific Aim 3: In a subset of individuals, to examine structural and functional changes that may occur in the brain following treatment with a high-CBD hemp product using multimodal magnetic resonance imaging (MRI) techniques.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Cannabis sativa has been used medicinally for a range of disorders for thousands of years, including anxiety. Cannabis is comprised of more than 100 cannabinoids; D^9-tetrahydrocannabinol (Δ9-THC) is the major psychoactive constituent, and cannabidiol (CBD) is the major non-psychoactive constituent that has been touted to have a variety of potential medicinal benefits. Industrial hemp is a variety of the *Cannabis sativa* plant, which until recently was grown specifically for industrial uses, such as textiles. Hemp has much lower concentrations of THC than cannabis, defined as THC<0.3% by weight. In recent years, some hemp strains have been bred to produce particularly high concentrations of CBD with very low concentrations of THC, virtually eliminating the potential for intoxicating effects. Extracts from these hemp strains are manufactured into a variety of oils, capsules, sprays, etc., available in brick-and-mortar stores across the country as well as on the Internet.

Previous studies have demonstrated CBD's acute anxiolytic potential in both animals and humans. Recently, our group began the first ever clinical trial of a high-CBD compound for anxiety. This trial, studied under IND [redacted], examines the impact of a high-CBD, low-THC cannabis-derived sublingual solution on measures of anxiety, mood, quality of life, and cognition over a 4-week treatment period. Interim analyses completed on the first 5 subjects who completed the trial were extremely compelling; analyses indicate that patients reported a 68.29% reduction in anxiety symptoms on the primary outcome measure, the Beck Anxiety Inventory (BAI), from the baseline to final visit. The study product is very well-tolerated, with no serious adverse events occurring to date.

The proposed investigation will be the first of its kind to conduct a clinical trial of an industrial hemp-derived product in individuals with anxiety. Despite the recent interest in MC and cannabinoid-based products, the availability of hemp-derived products in all 50 states, and anecdotal evidence suggesting that hemp-derived products may have a profound anxiolytic effect, no studies have conducted a clinical trial of a hemp-derived product in individuals who suffer from anxiety. Further, none have systematically evaluated baseline and follow-up clinical state and related quality of life measures in individuals taking hemp-derived products, or assessed measures of cognition, brain structure and function before and after treatment using neuropsychological measures and neuroimaging. The recent passage of the Farm Bill of 2018 has resulted in the exclusion of industrial hemp-derived products (THC content <0.3% by weight) from the Controlled Substances Act (CSA). As such, it is now possible to conduct clinical trials on industrial hemp-derived CBD products, including those such as Charlotte's Web (CW), which many thousands of consumers have purchased in recent years. As such, we will assess a proprietary hemp-derived formulation manufactured by CW [redacted]; the custom formulation contains approximately 30mg/ml of CBD and 0.8 mg/ml THC. In addition to providing information regarding the potential efficacy of an industrial hemp-derived CBD product for anxiety, this study will allow the comparison of a NIDA-based product, studied in our other IND and which lacks ecological validity, to a product that many thousands of consumers have used.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This study is an investigation of 40 subjects who have expressed interest in using CBD for anxiety. Subjects will complete study visits at McLean Hospital. Following a preliminary phone screen and prior to any evaluation, all study subjects will be required to sign a McLean Hospital approved informed consent form that describes all study procedures. The phone screen includes questions related to medical history, substance use history, demographics, and screening questions from the OASIS (see below) to determine whether the subject has anxiety.

Individuals will be assessed at baseline and throughout 6 weeks of treatment with compounds administered as sublingual tinctures in a double-blind, randomized procedure: subjects will receive either a high CBD product or matched placebo. Each product will be analyzed and verified at an

outside lab for safety and potency. Subjects will self-administer 0.5 ml (15mg/ml) of CBD or placebo sublingually two times daily. At each weekly visit, individuals will complete clinical scales and have a check-in with study staff. Neuropsychological testing will be performed at baseline and the final visit in order to assess cognitive performance. Buccal swabs will be collected for DNA analysis from all participants in the double-blind phase. Finally, a subset of individuals will receive an hour-long MRI scan at baseline and the final visit, with both resting state and task-related functional magnetic resonance imaging (fMRI) in each MRI session. In addition, a brief diffusion tensor imaging (DTI) sequence will also be acquired to examine white matter fiber tract integrity, and magnetic resonance spectroscopy (MRS) will be conducted to examine levels of certain metabolites in the brain. Subjects will complete study drug diaries manually (pencil and paper) or electronically.

In order to assess the efficacy of the dose chosen for the double-blind study, we will also conduct a small open-label trial of the CBD solution prior to initiating the double-blind study. This open-label trial will enroll up to 12 participants who are interested in using CBD, and who have anxiety. This trial will determine whether patients derive clinical benefits at the current dosage proposed for the active treatment arm of the double-blind trial. This trial will examine all components of the originally proposed study.

Subjects will be recruited through IRB-approved advertisements and flyers in regions that have approved medical marijuana. Additionally, medical marijuana healthcare facilities throughout New England, including CannaCare, Integr8, MMJ Physician Practice, and others, may also refer interested patients to contact the study recruitment line for further screening. These healthcare groups provide their interested patients who meet for general inclusion criteria with study recruitment materials. The total sample size for the double-blind study is 40 (20 CBD, and 20 placebo); up to 15 of each group (30 total) will also complete the MRI scanning protocol. For the open-label trial, the total sample size is 12.

Inclusion Criteria:

1) Subject has provided informed consent
2) Subject is 18 or older
3) Subject is a native English speaker or acquired English prior to age 5
4) Subject scores a minimum of 16 on the Beck Anxiety Inventory (BAI) OR a minimum of 8 on the Overall Anxiety Severity and Impairment Scale (OASIS) at the screening visit

Exclusion Criteria:

Subjects will be excluded if they report any of the following:

1) Non-native English speakers
2) Estimated IQ < 75
3) Meets criteria for DSM-IV classification of current substance abuse/dependence, psychotic disorder, bipolar disorder, or an eating disorder
4) A first-degree relative with a psychotic disorder
5) A history of head injury or loss of consciousness greater than 5 minutes
6) Currently uses marijuana or cannabinoid-based products more frequently than 1x/month
7) Female subjects will be excluded if they have a positive urine pregnancy test, or if they are currently breastfeeding
8) Presence of a serious medical illness, including liver, kidney, or cardiovascular disease, or neurological disorder
9) Allergy to coconut oil

10) Current use of valproate
11) Currently enrolled in other research studies or clinical trials involving interventions

Additional Exclusions for MR Component:

1) Claustrophobia or metal implanted within the body, body piercings which are not removable
2) Cardiac pacemakers, metal clips on blood vessels (also called stents), artificial heart valve, artificial arms, hands, legs, etc., brain stimulator devices, implanted drug pumps, ear implants, eye implants or known metal fragments in eyes,
3) Exposure to shrapnel or metal filings (wounded in military combat, sheet metal workers, welders, and others), other metallic surgical hardware in vital area, certain tattoos with metallic ink, certain transdermal (skin) patches such as NicoDerm (nicotine for tobacco dependence), Transderm Scop (scopolamine for motion sickness), or Ortho Evra (birth control), certain intrauterine devices (IUDs) containing metal
4) Poor vision, as subjects must have normal or corrected-to normal vision for viewing of cognitive challenge paradigms during fMRI protocols

Concomitant medications will be allowed and will be assessed on a case-by-case basis with the study physician; participants may be excluded if they are taking strong inhibitors or inducers of CYP3A4 (e.g. fluconazole, fluoxetine, fluvoxamine, ticlopidine, St. John's Wort, etc.), CYP2C19 (e.g. ketoconazole, erythromycin, etc.), or CYP2D6 (e.g. paroxetine, buproprion, quinidine, ritonavir, glutethimide, etc.). Dosing schedules may be adjusted in order to offset CBD administration with concomitant medications to decrease the likelihood of any drug-drug interactions. Subjects must have been on stable medication/psychotherapy regimens for at least 3 months prior to starting the study.

Subjects who participate in the open-label phase of the study will not be eligible to also enroll in the double-blind study.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

This study is designed to assess individuals who have expressed interest in using CBD for anxiety. Subjects will complete study visits at McLean Hospital.

A total of 52 (12 in the open-label phase, and 40 in the double-blind phase) female and male participants with anxiety, of minimum age 18, will complete a baseline visit including clinical ratings, an assessment of conventional medication use, quality of life measures, a neuropsychological test battery, a buccal swab sample, and optional neuroimaging (in a subset of participants who are eligible). Participants will subsequently be treated for 6 weeks with the CW sublingual solution. All participants will self-administer 0.5 ml (15 mg of CBD) of solution twice daily (BID). Participants will return to the laboratory or complete remote visits each week to complete clinical ratings and check in with study staff. After 6 weeks of treatment, participants will complete final clinical scales and quality of life measures, a complementary neuropsychological battery, and a corresponding neuroimaging component (where applicable). The open-label phase of the study is expected to take approximately 12 months to complete, and will assess the efficacy of the dose chosen for the double-blind study.

40 female and male participants will be enrolled in the double-blind phase. Study procedures will remain the same as the open-label phase, however participants will receive CW solution or placebo solution in a double-blind, randomized fashion. All participants will self-administer 0.5ml of solution BID for 6 weeks. The double-blind phase of the study is expected to take 24 months to complete.

Study Visits

Subjects will review and sign the approved informed consent form prior to engaging in any study procedures. A structured clinical screening interview (SCID-P or QuickSCID) will be administered, and demographic information, substance abuse/use, and medical histories will also be obtained and reviewed with the study physician. Study inclusion/exclusion criteria will be applied, and appropriate subjects will be enrolled and complete the rest of the study visit.

Open-Label Trial

Subjects will complete study visits at McLean Hospital. Following a preliminary phone screen and prior to any evaluation, all study subjects will be required to sign a McLean Hospital approved informed consent form that describes all study procedures. A structured clinical interview will be administered, and demographic information, substance abuse/use, and medical histories will also be obtained and reviewed with the study physician. Study inclusion/exclusion criteria will be applied, and appropriate subjects will be enrolled and complete the rest of the study visit.

For the first stage of the study, 12 individuals will be assessed at baseline and weekly for 6 weeks of treatment with sublingual CW solution in an open-label fashion: all subjects will receive the CBD product. Subjects will self-administer 0.5 ml (15mg) of CBD sublingually two times daily, in the morning and the evening, for a daily total dose of 30 mg CBD; if no clinical benefit (>15% reduction in BAI ratings) is evident at the 2-week visit, patients will be given the option to add an additional dose in the middle of the day to bring the total daily dose to 45mg CBD. At the weekly visits throughout the treatment period, individuals will complete clinical scales and have a check-in with study staff. In addition to clinical ratings and a check-in with study staff, neuropsychological testing will also be performed at baseline and week 6 in order to assess cognitive performance. A subset of individuals will receive an hour-long MRI scan at baseline and week 6, with both resting state and task-related functional magnetic resonance imaging (fMRI) in each MRI session. In addition, a brief diffusion tensor imaging (DTI) sequence will also be acquired to examine white matter fiber tract integrity, and magnetic resonance spectroscopy (MRS) will be conducted to examine levels of certain metabolites in the brain. Subjects will also provide a buccal swab sample for genetic analysis at the baseline visit; this will allow specification of genes related to degradative enzymes involved in the endocannabinoid system (e.g. FAAH, MAGL) and allow us to determine whether genetic profile can predict treatment response.

At the end of the baseline visit, eligible subjects will receive CBD solution. Subjects will be instructed on how to administer the compound in the morning and evening; they will be instructed how to draw 0.5 dropper of compound, deposit the amount in the dropper under the tongue, hold for 45-60 seconds, then swallow.

Double-Blind Trial

Individuals will be assessed in-person at baseline and weekly for 6 weeks of treatment with compounds administered as sublingual solutions in a double-blind, randomized procedure: subjects will receive either the CW solution or matched placebo. At the weekly visits throughout the treatment period, individuals will complete clinical scales and have a check-in with study staff.

In addition to clinical ratings and a check-in with study staff, neuropsychological testing will be performed at baseline and week 6 in order to assess cognitive performance. Finally, a subset of individuals will receive an hour-long MRI scan at baseline and week 6, with both resting state and task-related functional magnetic resonance imaging (fMRI) in each MRI session. In addition, a brief diffusion tensor imaging (DTI) sequence will also be acquired to examine white matter fiber tract integrity, and magnetic resonance spectroscopy (MRS) will be conducted to examine levels of certain metabolites in the brain. Subjects will also provide a buccal swab sample for genetic analysis at the baseline visit.

At the end of the baseline visit, eligible subjects will be randomized to either CW solution or placebo using a standard alternating procedure in accordance with the McLean Pharmacy. Subjects will be instructed on how to administer the compound, as described above.

For both the open-label and double-blind trials, the baseline and the final study visits are estimated to take approximately 3-4 hours, with the weekly visits in the interim estimated to take approximately 1 hour, and 15 minutes for phone check-ins, for a total of approximately 10-12 hours required to complete all possible visits. Urine samples will be collected at every other visit (Visits 1, 3, 5, and 7) to measure THC via GCMS (Quest Diagnostics) and to monitor for the presence of other substances throughout the study. Female subjects will be informed that their sample will also be used to confirm negative pregnancy (HCG) status; if at any point their urine tests positive for HCG, they will be excluded from the study. We are currently in communication with several groups that may be able to assess for CBD in urine; we hope to utilize one of these groups to quantify CBD in urine throughout the study.

Subjects will be given the option to complete daily study drug diaries manually (pencil and paper) or electronically. Adverse events and side effects will be assessed at weekly study visits and phone check-ins and all subjects will be advised to call study staff if they experience any adverse events.

Clinical Ratings

The Structured Clinical Interview for DSM-V Patient Version (SCID-P) and the SCID-P Substance Abuse/Dependence Module or the Quick Structured Clinical Interview for DSM-V Disorders (QuickSCID) will be administered to all study participants during visit 1 by the Principal Investigator, a Clinical Neuropsychologist or trained Clinical Research Assistant. Subjects will also complete clinical rating scales and questionnaires that have been shown to provide reliable estimates of current clinical state and are easily administered. They will also complete quality of life measures. All subjects will be given the following measures at the baseline and final visits that take approximately one hour to complete: [redacted]

[redacted]

Subjects will also complete a subset of these measures, specifically the anxiety and mood-related measures [redacted], along with the SEQ, at each weekly visit. An Abuse Liability Rating Scale (ALR) will be completed at V3 and V7.

Please note that if suicidality is endorsed spontaneously, on any of the clinical scales, or during the SCID or weekly check-ins with study staff, the patient will be immediately assessed for suicidality risk. Please see "Suicidality SOP" attachment for further information.

Neuropsychological Assessment

In addition to the clinical rating scales, the proposed investigation also includes a brief battery of neuropsychological tests to examine the potential effects of CBD on cognition in subjects with anxiety. Individuals will complete neuropsychological assessments at two time points; at baseline at after 6 weeks of treatment. The neurocognitive battery is primarily designed to evaluate frontal, executive, and memory functions as well as general intellectual capacity. The neuropsychological measures will be administered by a trained psychometrician and were chosen because they are standard, well-known measures that can be administered and scored reliably. Measures to be administered at baseline and both follow-up visits include the [redacted]. The neurocognitive assessment battery will take approximately 1.5 hours to complete. Many of these tests, including the [redacted] have alternate versions to use at the follow-up visit, in order to reduce the likelihood that subjects remember portions of the assessments from baseline.

Buccal Swab

Buccal swab samples will be collected at the baseline visit using Endo-DNA kits and used for genotyping.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Standard of care for anxiety treatment includes medications, such as antidepressants, buspirone, and benzodiazepines, as well as psychotherapy. This study is an investigation of a plant-derived compound that has promise in the treatment of anxiety. Subjects will not be asked to change their current treatment regimen to participate in this study (i.e. discontinue other medications); this study will add CBD to their current regimen.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Risks to subjects will be minimal throughout this study; please see below for detailed explanation of foreseeable risks and discomforts. The components of this study, including the clinical rating scales, neurocognitive tasks, and MR scanning have previously been used by the investigator in multiple studies. The administration of CBD will be low risk due to the add-on design of the study; patients will proceed with their treatment as usual, with CBD or placebo added to their medication regimen. See below for a detailed explanation of the risks of CBD administration in this population.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

The side-effect profile of CBD is extremely low, and adverse events are not anticipated. The daily dose is the same as another protocol using a cannabis-derived sublingual solution ([redacted]), and no serious adverse events have been reported in that study. Subjects may withdraw from the study at any time and for any reason. A subject's participation in the trial will end if they report adverse effects of CBD or placebo administration and wish to leave the study, or if study staff determine that study termination is appropriate due to adverse events. Additional termination criteria include: subject does not use solution as directed; subject sustains a significant head injury; any study exclusions are met (i.e. change in medical status, pregnancy, etc.)

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Risks Associated with Neuropsychological and Clinical Assessment/Rating Scales

Although unlikely, it is possible that during the structured assessment or rating scales, subjects may become distressed when recalling periods of their lives or their current mood state. Subjects may also become frustrated during the neuropsychological testing. Subjects are informed that they can take a break and/or can choose to stop answering questions at any time. To mitigate any risks associated with the neurocognitive assessment or clinical ratings, clinical staff will be available to evaluate and advise the subject during study visits.

MR/fMRI/DTI/DKI/MRS

Currently, there are no known risks associated with fMRI, MRI, DTI/DKI, or MRS scanning in the 3T scanner, however, there are some areas of concern that must be addressed. First, participation in an MRI study requires subjects to be exposed to strong magnetic fields, the long-term effects of which are unknown. The magnetic fields also require caution given the risk of attraction of ferromagnetic metal objects by the high strength magnetic field. Second, some subjects express discomfort by the relatively confined space within the bore of the MR scanner.

Finally, some subjects find the scanning experience unpleasant because of the noise of the gradients during MRI image acquisition. Each of these risks is present for a clinical MR scan, which are not increased by the research project proposed in this application.

CBD Administration

CBD has been shown to have an extremely low side effect profile and since the total amount of THC will not exceed 0.3% by weight, we do not expect significant side effects or psychoactive effects. CBD is not a scheduled substance, and there is no risk of intoxication or addiction to CBD. As with any clinical trial, there are risks of experiencing side effects from the administration of CBD or placebo; these side effects are very rare. Cunha et al. (1980) reported no signs of toxicity or serious side effects; in this two-part, placebo-controlled, double blind study, healthy volunteers were given 3 mg/kg of CBD or placebo per day for 30 days, and patients with epilepsy were given 200-300mg CBD or placebo per day for 4.5 months. The total dose of CBD per day for the current study will be 30mg – thus, we expect no significant side effects. Other studies have reported no adverse effects of CBD in patients with Huntington's disease, schizophrenia, and Parkinson's disease after repeated administration (Consroe et al. 1991; Leweke et al. 2012; Zuardi et al. 2006 and 2009). Subjects will have the opportunity to report adverse effects at their weekly check-in visits via direct contact with the PI and study staff. This weekly reporting will reduce the likelihood that subjects experience significant negative side effects for any significant period of time, and the PI as well as they study physician will be reachable by page 24 hours a day 7 days a week.

Sublingual solutions are unlikely to be viewed by the public as analogous to recreational smoked marijuana, thus decreasing the risk of the subject experiencing any potential negative appraisal arising from perceived notions associated with marijuana use while partaking in this study.

The safety of CBD administration in pregnant women and fetuses is unknown. Female participants capable of child-bearing will be asked to provide a sample of urine before the study is begun and at each subsequent study visit in order to screen for pregnancy. If the pregnancy test is positive at any point during the study, the subject will be immediately disqualified and participation in the study will cease. Participation requires that the participant uses contraception methods (such as abstinence, diaphragm, condom, or an intrauterine device) to prevent pregnancy for the duration of the study. The participant will be asked to notify study staff immediately if she misses a period or thinks she might be pregnant. In this case, the participant may have to withdraw from the study.

DNA Collection

The primary risk of collecting and examining genetic information is the remote possibility of future genetic discrimination. It is possible that these data or the buccal swab samples from which they were derived could be stolen, analyzed, and used to reveal sensitive information that may in turn lead to insurance coverage or employment denial. There is a very remote possibility that enough information could be stolen to help identify a person, exposing individuals to any risks that result as that identification. Procedures described below minimize the possible breach of confidentiality.

Protection of risks: To reduce the possible risk of a breach of confidentiality regarding genetic material, the informed consent will include a specific section addressing risks associated with collecting genetic material. The consent form will have choices regarding the permissible uses of his/her DNA. These range from "restriction to this study only" to "any future research use by the study investigators" (provided that any future study is approved by an IRB). One of the choices must be initialed by the participant. Participants will also be informed that they may have their DNA samples destroyed at any time, and will provide the necessary information on how to inform investigators to do this.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

There may be no direct benefits to the subjects; however, based on previous research, it is reasonable to expect that some subjects may experience an improvement in clinical state or quality of life related to a reduction in anxiety.

It is reasonable to expect that this study will contribute to overall knowledge in this field and potentially provide benefits to society in general through improvements in treatment and management as a result of this increased level of understanding.

Subjects are informed that there may be no direct benefit to them from participating in this study. Subjects may benefit from knowing that the results of this study may improve the future care of people prescribed medicinal marijuana, particularly those with anxiety.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

No subjects will be excluded on the basis of race, sex, ethnicity or sexual orientation.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

All subjects must be native English speakers because several of the cognitive tasks require English as the native language in order to accurately assess cognitive state.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Recruiting and enrollment will be the responsibility of the McLean study coordinators. Subjects will be recruited from a number of sources, including IRB-approved flyers and post cards, as well as online postings (including Rally) and via RPDR messaging. Medical marijuana certification facilities and anxiety clinics may also refer interested patients to contact the study recruitment line for further screening. Potential subjects for this study must be capable of understanding the nature of this study as well as the discomforts and potential benefits. All subjects will be given as much time as they want to consider their participation in the study and ask any questions they may have before being asked to sign the consent form.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

A tiered payment system will be used for a payment of $75 at visit 1, $30 each at visits 2, 3, 4, 5, and 6, and $75 at visit 7 for a total of $300; if termination occurs during any point of the visit, subjects are compensated at a rate of $25 per hour. Subjects who participate in the scanning component of study will receive an additional $75 at visit 1 and visit 7 for a total of $450. Subjects will receive a completion bonus of $50 if they complete the study, for a total of $350 or $500, depending on whether they receive MR scanning. Subjects may withdraw from the study at any point; and will still receive payment for the portion of the study they completed at a rate of $25/hr.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Written, informed consent will be obtained from all participants following a screening interview to determine eligibility. All subjects will be required to give informed consent and must understand all procedures prior to their participation in the study. Consent will be obtained by the principal investigator, Dr. Staci Gruber, or the licensed physician investigator on the protocol, [redacted]. If consent is obtained by Dr. Gruber, a licensed physician investigator will review and sign off on patient enrollment. A physician will also be available if the patient has any additional questions during the consent process. The consent form will include a description of the study, information about procedures, and assurances of confidentiality. A member of the research staff will explain the consenting procedure and be available for any questions that arise from the consent form. Prior to signing the informed consent, subjects will be asked if they have any questions regarding the conduct or design of the study. A copy of the signed consent form will be given to the study subject, and a copy placed in their research record. All subjects will be reminded that their participation is completely voluntary, and may withdraw or discontinue the neuropsychological evaluation at any time. The informed consent will be approved by the McLean Hospital Institutional Review Board, which monitors study progress, safety and outcome on a regular basis. All signed consent forms will be kept in the subject's case report form in room 204 of the Neuroimaging Center under lock and key.

Remote Consenting Process

We will remotely consent patients by one of the two following options. The first option will consist of consenting via REDCap using the MGB consent template. The second option is to send the participant the consent form ahead of time for their review, consent them over the phone, and have the participant physically sign or e-sign the consent form and either scan or take a photo of all pages, and send to us; this will be signed by the investigator, and a copy will be provided to the participant. In-person written consent may also occur in rare circumstances. Each subject's file will contain a note to file describing the procedure followed.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:

https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:

Informed Consent of Research Subjects:

https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Data analyses will be conducted on the open-label phase of the study prior to initiating the double-blind phase in order to ensure that patients derive clinical benefit from the dose selected. Specifically, in conjunction with [redacted], we will assess clinical response after the first 5 patients have completed their 6 week trial. If we do not see clinical improvement based on a review of clinical scales, subjective reports and performance, we will consider increasing the dose to 1 droppers two times a day for a total of 60 mg CBD per day. Clinical improvement will be defined as a 15% reduction in BAI scores from baseline. Findings will be used to inform the double blind phase of the study, which would not begin until adequate dose/response is achieved. An amendment would be submitted to the IRB for approval prior to adjusting the dose of CBD.

In the unlikely event that an adverse event occurs, it will be reported to the primary investigator and the Institutional Review Board's guidelines will be followed to ensure adequate reporting and response. All adverse events will be reported to the Partners Healthcare Internal Review Board for their records. There are currently no plans to utilize a Data Safety Monitoring Board (DSMB) due to the extremely low side-effect profile of CBD, but if the IRB deems that an independent DSMB is necessary, the investigators would be happy to suggest individuals who are appropriate or to consider outside suggestions from IRB members.

Subjects are required to have a structural MRI scan of clinical quality at least once per year at McLean Hospital that is reviewed by a board-certified radiologist or neurologist and a clinical report is generated usually within 2-4 days. If the subject has not received a structural clinical scan in the past year, one will be obtained for the present study. Subjects will not receive more than one structural clinical MRI within a given 12-month period unless a follow-up scan is recommended by the radiologist who reads the scan. Abnormal reports are reviewed by the Clinical Director of the McLean Imaging Center (MIC), [redacted] and forwarded to the Principal Investigator, in this case, Dr. Gruber, and the designated study physician. If an abnormality is present, the study physician and PI will coordinate the process of contacting the subject so that an appointment can be made to discuss the findings. The MIC Clinical Director may also assist with this process when requested and appropriate. If a follow-up scan is recommended by the radiologist, we will offer the subject a cost-free repeat scan (with contrast if indicated). In all cases we offer a copy both of the clinical report and the MRI scan (on film or cd) to subjects to take to their primary care or other consulting physicians, at no cost.

FMRI, DTI/DKI, and MRS data collected will be processed with software available in the Neuroimaging Center. Echo planar images will be analyzed off line using a semi-automated fMRI data analysis tool and a motion correction algorithm developed on-site at McLean. Measures of

signal intensity will be derived by averaging the signal measured in all pixels in each region of interest (ROI) for each time point during the task activation period.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

In the unlikely event that an adverse event occurs, it will be reported by the primary investigator to the Institutional Review Board, and the IRB's guidelines will be followed to ensure adequate reporting and response. All adverse events will be reported to the Partners Healthcare Internal Review Board for their records.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

Regulatory binders are kept for all studies at McLean Hospital in order to constantly monitor investigations and ensure that all data is collected safely.

The principal investigator will be responsible for monitoring and ensuring the integrity of the data and adherence to the IRB-approved protocol. They will review any questions or concerns regarding data, and will review each signed consent form for the study.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Confidentiality of information collected will be maintained with the assignment of an identification number or code, which will be used in place of subject names in all data analyses and reports. Computer systems are located in the Cognitive and Clinical Neuroimaging Core. Keys showing the assignment of identification numbers to subject names will be stored with subject files in [redacted] under lock and key. All of the data that is collected will be kept for a minimum of seven years once the study has been completed. Only the Principal Investigator, Dr. Staci Gruber, her research staff, and the study collaborators will have access to the data that is collected.

All subjects will be required to give informed consent and must understand all procedures prior to their participation in the study. Subjects are informed of their confidentiality and privacy rights in the informed consent form. To ensure that subjects' rights and safety are protected during the conduct of this research study, subjects consent to the inspection of their medical records by specifically authorized monitors. Such monitoring may be performed by the Human Research Protection Program of McLean Hospital, or by the FDA or other involved federal agency.

Subjects are informed that all the information obtained in this study will be used for research investigational purposes only. Name of subjects will never be publicly disclosed at any time. Subjects will not be identifiable in any publication that may arise from this research.

Subjects will receive a copy of the consent document to keep as well as a copy of the "Partners Healthcare Notice for Use and Sharing of Protected Health Information." Subjects will be informed that this research will be conducted and administered in compliance with all state and federal laws.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

In some cases, urine samples may be sent to Quest Diagnostics to assess recent substance use. The samples will be labeled with the subject's initials, date of birth, and study ID.

Data collected during the study may be sent to [redacted] in order to provide public health context to our research findings. A Data Sharing Plan is on file detailing the method of sharing, security provisions, etc.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Specimens will not be stored off-site for future use not described in the protocol.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

N/A

STATISTICAL APPROACHES

All statistical analyses will be conducted using IBM SPSS Statistics (version 28). Data will be screened for outliers and any data points more than 2 standard deviations from the group means will be excluded. Additionally, data will be screened for skew, kurtosis, non-normality, and homogeneity of variance. If the assumptions of parametric inferential analyses are not met, the appropriate non-parametric analyses (e.g. Wilcoxon-Signed Rank Test) will be performed. Descriptive statistics will be used to characterize the demographic data. Baseline clinical and neuropsychological data will be assessed using 2-tailed paired *t*-tests to compare follow-up timepoints to baseline values. When needed, Bonferroni corrections for multiple comparisons will be utilized.