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Research Subject – Part 1 (R61 Group) Informed Consent Form

Title of Study:	Randomized placebo-controlled trial to determine the biological signature of cannabidiol as a treatment for social anxiety disorder s22-00568
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1. About volunteering for this research study

You are being invited to take part in a research study. Your participation is voluntary which means you can choose whether or not you want to take part in this study.

People who agree to take part in research studies are called “subjects” or “research subjects”. These words are used throughout this consent form. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. You may also decide to discuss this study and this form with your family, friends, or doctor. If you have any questions about the study or about this form, please ask us. If you decide to take part in this study, you must sign this form. We will give you a copy of this form signed by you for you to keep.

2. What is the purpose of this study?

The purpose of this research study is to understand to how cannabidiol (CBD) works for patients with social anxiety disorder (SAD). Specifically we want to understand the behavioral and neurological (brain) changes that contribute to reduction in SAD symptoms with CBD treatment compared to placebo. SAD is a mental health disorder with specific core features, such as worry and anxiety about being judged, negatively evaluated, or rejected in social or performance situations.

Cannabidiol is a compound found in the cannabis plant. It has been shown in numerous studies to be safe and well tolerated. Evidence from numerous studies found oral CBD in repeated daily doses ranging up to 6000 mg per day was safe and well-tolerated, and did not produce adverse mood effects. Further, CBD did not exhibit potential for addiction in a human study. Hemp-derived CBD has not been reported to cause a ‘high’ or other mind-altering or negative mood effects commonly associated with tetrahydrocannabinol (THC). The Food and Drug Administration (FDA) has approved one CBD-based drug called Epidiolex as a

treatment for rare and severe seizure disorders that affect children. CBD is considered investigational in this study because it is not FDA-approved to treat SAD. We are comparing CBD to placebo, which looks just like CBD but contains no active ingredients.

We are asking you to take part in this study because you are between the ages of 18 and 45 who described experiencing symptoms consistent with Social Anxiety Disorder. This study is being paid for with grant funds from the NIH (National Institutes of Health), as well as supplemental funding from Ananda Scientific. This study will be done in 2 parts. The first part will be done to determine an optimal dose of CBD for SAD. The second part will be done to replicate what we learn about CBD for SAD and compare the optimal dose from part 1 to placebo. In both parts of the study, we will also study how CBD is processed in the body over time. You are being asked to participate in part 1.

3. How long will I be in the study? How many other people will be in the study?

If you qualify, your total participation time in this study will be about 1 month.

About 60 subjects will take part in this research study at NYU over a 2-year period.

4. What will I be asked to do in the study?

If you choose to take part in the study, we will ask you to sign this consent form before you have any procedures with the study staff that are part of the study.

- Step 1 of the study includes screening and, if you qualify, baseline assessments which will be completed in 1 to 4 weeks.
- In Step 2 of the study you will be randomized to taking CBD or placebo for approximately 3 weeks, including one safety assessment and a stress test after two weeks of taking the study drug.
- Step 3 will consist of two consecutive days of Experimental Visits at the end of the three weeks. This 2-day Experimental session will include one day of training outside of the fMRI scanner followed by a second day done inside the fMRI scanner.

This study is a randomized study. This means, like choosing from a hat, you will be assigned to one of three treatment groups. You will have a 1:1:1 chance of getting CBD 400mg (200 mg twice daily), CBD 800 mg (400 mg twice daily), or placebo.

This study will compare behavioral and brain changes in participants with SAD who take CBD with those who take the placebo.

The fMRI machine uses a magnetic field to produce pictures of your brain while you are asked to do different tasks. This machine is routinely used by scientists to study the brain. When you are in the fMRI scanner, it will take pictures (images) of your brain while you are performing a task. This procedure does not use any radiation (x-rays). During the fMRI, you will be asked to lie quietly on a table that slides into a tunnel shaped machine. The machine is slightly wider than your body. The top and sides of the tunnel will be very close to your body. The machine makes knocking and beeping sounds as it takes pictures of your brain. Earplugs will be provided to reduce the sound and to protect your hearing. During the scanning session, the investigators will be able to speak to you while you are in the machine. You will also be able to hear and speak to them at all times. We can stop the procedure at any time, if necessary.

During your participation in the study, we ask you not to initiate any new psychiatric medications or additional psychological interventions. If you wish to commence any of these other forms of treatment, you may withdraw from the study at any time.

Over the course of the study, the study doctor may wish to contact your mental health doctor/counselor in order to confirm information about the medications you may be taking, or for other safety reasons.

Do you agree to let the study doctor contact your mental health doctor/counselor in order to confirm information about your current medications or other safety reasons?

☐**YES** ☐**NO Initials**_____

If you checked "YES" in the box above, we will ask you to provide us the name and contact information of your mental health doctor/counselor, which we will document in your research record.

Detailed Visit Information:
On the first assessment visit, we will determine your eligibility and explain to you details of the study. If you are eligible, we will have you come back for a second visit to fill out several questionnaires and we will randomize you to one of the three conditions, CBD 400mg (200 mg twice daily), CBD 800mg (400 mg twice daily), or placebo. On the fourth and fifth visits, you will answer several questionnaires and participate in a stress test. On the fifth and sixth visits, you will go through an emotional learning task and a neuroimaging scan. We will examine your physiological response (skin conductance response, which measures sweat from the palms of your hands) and your brain responses using a functional Magnetic Resonance Imaging (fMRI) machine. These visits are described in greater detail in the following paragraphs.

Step 1: Screening Phase (Visit 1)

Visit 1 – Screening Visit(s)
This visit will take about 3 hours and may be split up on different days. The following things will happen during your Screening Visit:

- A study clinician will explain the study to you. You will be able to ask any questions or voice concerns that you may have regarding the study.
- The study clinician will ask about your past and present psychiatric symptoms, any past or present medical illnesses, and any medications you have been taking (including over the counter medications).
- You will have a physical examination, including an EKG, urine and blood tests to evaluate whether there are medical conditions that prevent study participation. We may also ask your permission to speak to your doctor.
- You cannot take part in this study if you are pregnant or are planning to become pregnant. If you can become pregnant, you will have a urine pregnancy test. At least one form of highly effective contraception must be used by women of childbearing potential and by males during the study.
- Urine Drug Screen: we will test your urine for drugs, including illegal drugs like cocaine, marijuana, amphetamines and others. If your urine shows you have taken any of these drugs, you cannot be in the study. The results of the urine drug test will NOT become part of your medical record.
- Your vital signs (heart rate, breathing rate, blood pressure, and temperature) will be taken
- You will complete a demographics form that asks you about your age, gender, race and ethnicity, etc. and, if you are female, you will also complete a questionnaire regarding your menstrual cycle or menopausal status.
- You will be asked whether you have had thoughts about harming yourself or have tried to harm yourself.

Portions of the screening visit (consenting, psychiatric assessments, medical history) and some other assessments during the study period may be conducted remotely via Webex in some circumstances. This will be at the discretion of the research team, such as in the circumstance of weather, possible COVID-19 exposure, or as needed for timely scheduling. Webex will only be used if deemed necessary by the research team.

If the screen is conducted virtually – the procedures will be broken down into two visits. Virtual procedures may

include e- consenting and discussing your past and present psychiatric symptoms. Reviewing any past or present medical illnesses, and any medications you have been taking (including over the counter medications) may occur virtually or in person. The portion of the visit that includes the physical examination, vitals, pregnancy test (if applicable), and urine drug screen will occur in person.

After these assessments are completed we will tell you if you are eligible. If you are eligible, we will schedule your next assessment visit. If you are not eligible for this study, we will tell you why. We may tell you about another study that you may qualify to take part in or we will give you an appropriate treatment referral.

Step 2: Assignment to Study Group, Treatment Phase and Study Assessments (Visits 2-4)

Visit 2: Group Assignment:
After confirming your eligibility from Visit 1, we will schedule a brief remote assessment to ask you a few more questions about your psychiatric symptoms and then we will randomly assign you (by chance) to one of 3 study conditions:

1. CBD (400 mg): 200mg taken twice daily for 3 weeks
2. CBD (800 mg): 400mg taken twice daily for 3 weeks
3. Placebo taken twice daily for 3 weeks

Which condition you are assigned to will be done by a computer. Neither you nor the researchers will choose what condition you will be assigned to. You will have a 2:1 chance of receiving CBD treatment or placebo respectively.

After you are randomized, you will come in-person for the remainder of your baseline visit. At this baseline visit, you will be asked to fast for 8 hours prior to the visit, provided with a light meal before the drug is administered and have your blood drawn twice. This visit will take approximately 3 hours.

Study Drug Adherence:

We will track your adherence to the prescribed treatment through a secure video recording system. We will ask you to use this platform to record yourself each time you take a study pill. This study will use a mobile application to gather this information for the researchers as part of this study. This mobile application is provided by Scene Health and there are terms of use that the vendor requires of all users. You will need to review the app maker's terms of use and privacy policy, which we will provide to you. The maker of the app may retain some of the data collected through the mobile application even after the study ends. If you do not want this data collection to continue by the maker of the app after the study ends, you will need to de-install/discontinue use of the mobile application. The research team can help explain how to do this. Any data that is stored by the app or sent to the app maker is not under the control of NYU Langone Health, which means that NYU Langone Health cannot directly edit or otherwise delete it.

After study completion, the study team will notify Scene Health and issue a request for all videos and files to be deleted from their HIPAA compliant server and application. Scene Health will send the study team all files and documentation with participant information to be transferred to NYU's secure servers before deletion from their server. Afterwards, we will request a letter or email notification from Scene Health confirming the deletion of all participant files from the Scene Health server. It is up to Scene Health to delete these files.

At this visit, we will also collect blood samples twice during your visit procedures before and after your first dose of the study medication to examine the concentration of CBD and THC in your blood.

Visit 3: Study Assessment Visit:
The study assessment visit, which will take approximately 30 minutes, will be the same for all subjects regardless of treatment group. The assessments in this visit will be similar to those in your Visit 2 and will take place approximately 2 weeks after you begin treatment. At this assessment, which may be in person or virtual and can be during visit 4, the following things will happen:

- A study doctor will ask about your psychiatric symptoms and about how you are doing with the drug (any side effects)
- We will ask you to complete standard questionnaires and rating forms that will be used to evaluate your progress. The questionnaires and rating forms are about your anxiety symptoms, your general health, mental health, medications you are taking, quality of life, emotional health, and mood. They will also ask about your medication adherence.

Visit 4: Stress Test:
This visit will occur within 0-3 days of Visit 3. During this visit, you will undergo assessments for study drug treatment effect as assessed during a 15 minute psychological stress test. We will also take two blood samples at this visit and provide you with a light meal. You will be asked to fast for 8 hours prior to the visit. This visit will take approximately 3 hours to complete.

Step 3: Endpoint Experimental Assessments (Visits 5 & 6)
Experimental and Neuroimaging Visits (2 consecutive days):

For the first day of the experiment, you will come to our center at One Park Avenue after fasting for 8 hours prior to the visit. In this experimental day, you will be asked to pay attention to images displayed on a monitor. We will use a half-second uncomfortable but not painful electric shock to your foot. Two small electrodes (sensors) will be attached to your foot. The electrodes are made of a small piece of metal that is attached to a cable. The electric shock feels like, to most people, an uncomfortable tingling sensation. In the first part of this experiment, we will find the level of current that you find is very uncomfortable, but not painful. To do this, we will begin at a low level that you will not be able to feel. We will slowly increase the shock levels with your permission until you find the level of the current to be very uncomfortable, but not painful. During the rest of the experiment, the level of current that you will experience will not be changed by us (we will not increase it or decrease it).

The purpose of the electric shock is to create a situation in which emotional learning may occur. This means that you will learn that the shock may always, or most of the times, follow a specific picture. When we thereafter show you the picture, you may become a bit nervous because you now learned that this given picture predicts the occurrence of the shock. We will then show you a series of pictures of different rooms. After you see some of the pictures, you may receive a half-second electric shock to your fingers at the very uncomfortable level that was selected earlier. You will receive no more than twelve of these electric shocks. Wires that are attached to the surface of your hands will measure your body's responses to the pictures that you see. The small stick-on pads with wires attached (electrodes) that are attached to your hands will be connected to a computer that can detect how nervous you are by measuring the amount of sweat in the palm of your hand. This procedure will take about 1 hour.

The entire visit will take about 3 hours. We will also take two blood samples at this visit 120 minutes apart and provide you with a light meal

Exactly one day after this (visit 6), we will ask you to come to the NYU Langone Ambulatory Care Center, 159 E 53rd Street for the second experimental day. This visit will start with a urine pregnancy test, if you are female. If you are pregnant, you cannot take part in this study since we do not know the risk of magnetic imaging on the developing fetus. We will ask you to take part in two experiments during the scan. One will involve looking at pictures. The second experiment will be similar to the one you did during the first Experimental day, except this time you will be in an fMRI scanner.

Day 1 and 2 Conditioning and Extinction Experiment: We will place electrodes on your hands to measure your body responses. We will also place the electric shock electrodes on your foot. Following that, you will be shown the same pictures of the rooms that you saw during the first Experimental day on the computer monitor. During this visit, you may or may not receive electric shocks. However, if you do receive the electric shocks, you will receive no more than ten of these shocks. The shocks that you may receive will be at the same uncomfortable level that you received during the first Experimental day. The first day will be out of the scanner and the second day will be in the fMRI scanner.

Day 2 only Faces Experiment: During the first part of the fMRI scan, we will have you look at faces on a screen that will each be presented twice for a few seconds each time. We will ask you to rate each face based on how fearful the expression looks to you.

This visit will take approximately 2 hours.

Audio Recording:
Your assessments will be digitally audio-recorded. This will allow us to monitor that ratings are being done accurately by our clinical staff working on the study. Making an audio recording of each session is part of this study. By signing the separate audio consent form you are agreeing to have your sessions audiotaped for study related purposes. Your consent to be audio recorded may be withdrawn at any time and the recordings can be erased either during or after the session. However, if you withdraw your consent to be audio recorded, you will not be eligible to continue to receive study treatment. If you wish to withdraw your consent and would like your recordings to be destroyed, you may inform the project staff either verbally or in writing.

People who will listen to the recordings include your study clinicians and their study-approved supervisors at NYU Langone Health. Other study clinicians and/or people who are learning the study protocol may also hear some segments of the recording. Approved study staff at NYU Langone Health will listen to selected recordings in order to evaluate whether the assessments are being done according to study guidelines.

Audio recordings may be shared electronically with approved investigators working on this study. Transmissions will be done only through secure channels that give access for listening within the NYU firewall. The audio file will be labeled with a code and will not be labeled with any information that could be used to identify you, such as your name or your date of birth. We plan to keep these recordings on an electronically secure, password protected hard drive in a locked room for no longer than 5 years after the primary study is completed (approximately 10 years total) to allow enough time for the study investigators to complete approved study of the recordings.

Any identifiable private information or specimen collected or used for the purposes of this research will not be used or distributed for future research studies.

Please note, because of the ongoing COVID-19 pandemic, all institutional practices regarding infection prevention will be adhered to.

Participation in other studies
In order to minimize risk and to assure your health and safety, it is important for us to assess whether you are participating in other research studies. We will ask you to inform us of the research studies in which you have participated *in the past year that involve medication, investigational drugs, or psychotherapy*. We will include the dates of participation, principal investigator name, and brief information about the study in your research record. By signing the consent form, you are also agreeing that we may contact the study staff of research studies you are currently participating in so that we can coordinate the studies if necessary and assure your safety.

OPTIONAL: Contacting You in the Future:
We may wish to contact you in the future about related research studies. Is it okay to contact you in the future?

Do you agree to be contacted in the future?

_____YES, it's OK to contact me in the future
(initials)

_____NO, don't contact me in the future
(initials)

5. What are the possible risks or discomforts?

Psychological Stress
There is a risk of a negative emotional reaction to the recruitment, structured interviews, and questionnaires. You could develop mild to moderate emotional discomfort or frustration associated with psychiatric interviewing or filling out questionnaires. You may experience subjective distress during treatment. Some people may feel embarrassed or uncomfortable while participating in the stress test. You may feel uncomfortable or you may become upset when answering some of the questions in the questionnaires or during the interview. You may skip any questions you don't want to answer.

Cannabidiol (CBD) or Placebo
The available evidence suggests that CBD is safe and well-tolerated in human subjects. Oral CBD has been administered in clinical trials to both healthy volunteers and patients with various medical conditions, as single or multiple doses ranging from 10 mg to 6000 mg. In most of the studies CBD was well tolerated and no severe or serious adverse events (AE) were reported. Hence, CBD is generally considered to have a favorable safety profile.

In a study published recently involving healthy volunteers, oral CBD doses of up to 6000 mg (single administration) and up to 1500 mg/d (multiple dose) were associated with only mild or moderate AEs, and none resulted in the early termination of participation. The most common AEs in all the trial arms were diarrhea, nausea, headache, and tiredness. Diarrhea and headache were more common in subjects taking CBD compared with placebo.

The recommended dose of the FDA-approved Epidiolex® (oral CBD administered mostly to children to treat seizure disorders, Dravet Syndrome and Lennox-Gastaut) ranges from 5 mg/kg/day to 5 mg/kg twice daily (10 mg/kg/day). Occasionally 20 mg/kg/day have also been administered. Since the drug has only been approved recently, no post-marketing safety data is available, and the following information is based on controlled and uncontrolled clinical trials experience. The most common adverse reactions that occurred in Epidiolex®-treated patients (incidence at least 10% or at least 10 out of every 100 patients) and greater than placebo) were

- Sleepiness
- Decreased appetite
- Diarrhea
- Decreased energy
- Rash
- Difficulty sleeping
- Infections
- Increase in liver enzymes: CBD (in the form of Epidiolex™) has been reported to be associated with dose-related elevations in liver transaminases (ALT and/or AST). There also was a clear dose association: 8% (8 out of 100) elevations overall in the 10 mg/kg group and 16% (16 out of 100) in the 20 mg/kg group. Elevated liver enzymes do not necessarily signal a serious liver problem. There do not appear to be reports of CBD-treated patients who have experienced liver failure. Identified risk factors for transaminase elevation included taking other medications such with valproic acid (a medication used to treat seizure disorders, mood conditions and migraine headaches), and elevated baseline liver function tests. Most events of transaminase elevation occurred within 30 to 90 days after initiation of CBD treatment although rare cases were observed up to 200 days after initiation of treatment, particularly in patients also taking valproic acid. These abnormalities generally resolved with discontinuation of cannabidiol or dose decreases in cannabidiol or valproic acid, yet elevated levels also resolved spontaneously without changing the dose of CBD

- We will assess your liver function at screening as well as at 2- weeks

The CBD and placebo medications for this study are provided by ANANDA Scientific. Note that the specific drug product to be used in this trial has only been studied in healthy volunteers (and at lower doses than will be used in this trial) and has not been administered to patients previously. Also, note that this drug products is not Epidiolex™ (the marketed and approved CBD drug product) and is an experimental drug product. In a human safety study conducted on the formulation of CBD (A1002N5S) that will be used in this study, a total of 12 AE's occurred after the start of dosing. None were serious, all were considered mild, and none were considered related to the study drugs. The most frequent AE was headache (6/12, 50.0%) reported by 5 (out of the 15) subjects.

Since it is possible that there is a theoretical risk of adverse drug interactions between CBD and grapefruit

(in terms of grapefruit potentially increasing levels of CBD when the two are taken together), you are to avoid consuming grapefruit or grapefruit juice during the duration of the study.

Also note that concomitant use of alcohol may increase the risk of sedation and somnolence.

Blood Drawing
Occasionally there are risks associated with blood draws such as bruising, swelling, black and blue marks, fainting and/or infection at the site. You may also experience a decrease in hemoglobin and hematocrit (red blood cell number, called anemia) from having blood drawn frequently. Approximately 3 ounces of blood (6 tablespoons) per participant will be drawn for research purposes during this research study.

Fasting
Although not eating for 8 hours overnight is common, there may be some risks associated with fasting. In addition, although only 8 hours are requested for a fast, this may be longer if your schedule does not allow eating 8 hours prior to the visit. The most common side effects of fasting include: hunger, irritability, lightheadedness, mild headache and a reduced ability to concentrate (focus or pay attention) during periods of food restriction. However, many of these side-effects were reported when patients were also limiting their caloric intake (not eating as much food). If you experience any these symptoms, please tell the study staff right away.

Electrocardiogram (EKG)
The EKG test is a recording of the electrical activity of your heart and an EKG is harmless. The sticky pads (electrodes) that are placed on your chest can sometimes cause discomfort such as redness or itching. We may need to shave your chest before we attach these pads. Irritation from shaving also may occur.

Other Risks
MRI Risks:
Magnetic Field Risk:

MRI uses strong magnetic fields and radio waves to make images of the inside of your body. MRI does NOT involve high-energy radiation (like x-rays). For most people MRI is very safe. However, if you have anything made of metal on your skin or inside your body, MRI may not be safe for you, and you must tell study personnel before your scan. Also, if you have any electronic devices on the outside or inside of your body, you must tell study personnel about those too. Some things, like tattoos, may have metal materials in them even though you might not realize it. For this reason, study personnel will give you a checklist of things that have metal or electronic parts in them. You must read the list carefully before your scan and put a checkmark next to everything that applies to you.

The following paragraphs will describe the possible risks of MRI. To reduce many of these risks, you will be given an emergency squeeze ball to hold in your hand during the scan. If you feel any discomfort you should squeeze the ball. This sets off an alarm that the technologist can hear. The technologist will then

talk to you, and will stop the scan if you want. There is a microphone in the scanner so that you can communicate with the technologist. However, the scanner makes a lot of noise when it is running and the technologist may not always hear what you say. If you need to get the technologist's attention, you should squeeze the ball.

Remember, if at any point you feel uncomfortable and want to stop the scan, just squeeze the ball and tell the technologist.

Risks from metal

The strong magnetic field in the scanner will pull on things that contain certain types of metal. If someone takes a metal object into the scan room, it might fly towards the scanner and hurt you. For this reason, everyone (including you) must remove everything metal from their clothes and pockets before going into the scan room. Also, the door to the scan room will be kept closed during the scan to prevent unauthorized people from walking in.

If you have something metal inside your body, the scanner might pull on it and make it move. You must tell study personnel before your scan if you have anything metal inside your body.

Some types of metal might heat up when the scanner is running. If you feel any burning sensation during the scan, you should squeeze the emergency ball and the technologist will stop the scan.

Risks from electronic devices

If you have any electronic devices on the inside or outside of your body, the scanner might make them stop working properly. For this reason, you must tell study personnel before your scan if you have anything electronic on or in your body.

Burns

Metal is not the only thing that can cause burns in MRI. It's possible (although very rare) to get burned by touching the inside walls of the scanner or by making skin-to-skin contact. The technologist will give you a blanket or cushions so that you don't touch the inside walls of the scanner. You should also avoid letting your hands or legs touch each other. Remember, if you feel any burning sensation during the scan, you should squeeze the emergency ball and the technologist will stop the scan.

Tinnitus (ringing in the ears) and hearing loss

The scanner makes very loud sounds while it is running. You will be given earplugs or headphones to wear during the scan. Make sure you roll the earplugs tightly and let them expand in your ears so that they work properly. If the sound of the scanner is still so loud that it causes you discomfort, squeeze the emergency ball and tell the technologist. This is important because very loud sounds can cause ringing in the ears or even hearing loss.

Feeling warm or hot

The radiowaves used in MRI are like those your cellphone uses, but much stronger. Sometimes they are strong enough to make you feel warm (just like standing in bright sunshine makes you feel warm). MRI scanners are designed to try to avoid you getting too hot. However, if you start to feel uncomfortable, squeeze the emergency ball and tell the technologist.

Peripheral nerve stimulation (tingling or twitching)

The magnetic field inside the scanner changes very quickly while the scanner is running. If it changes too quickly, it can give you tingling sensations or make you twitch. MRI scanners are designed to try to avoid this. However, if you experience tingling or twitching, squeeze the emergency ball and tell the technologist.

Claustrophobia (discomfort in enclosed spaces)

Some people get panic attacks inside enclosed spaces. This is called 'claustrophobia', which means 'fear of confined spaces'. If you know that you are claustrophobic, tell study personnel before your scan.

Some people only find out they are claustrophobic when they have an MRI for the first time. If you feel anxious or panicky inside the scanner, squeeze the emergency ball and the technologist will get you out.

Quench
In very rare circumstances, the scanner can lose its magnetic field. This happens very suddenly and is known as a 'quench'. The helium that helps keep the magnetic field strong will then escape from the scanner. The scanner is connected to a vent so that the helium will go outside the building. However, if for some reason the vent doesn't work properly, helium might fill the scan room, making it difficult to breathe. In the very unlikely event of a quench, the technologists will get you out of the scanner immediately.

Incidental Findings
This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice a clinically significant and medical actionable finding. Should this occur, the finding(s) will be reviewed by a licensed radiologist and the PI will inform the subject of the results if necessary, within two weeks of discovery. A copy of the original image report will also be provided and the subject will be encouraged to follow up on the discovery with their treating physician. These possible finding(s) may or may not be significant and may lead to anxiety and to further work-up by the subject's physician.

Below we are asking you to indicate whether or not you would like to know about any incidental findings as described above. Please initial one of the options below to confirm whether you would like to be informed of any incidental findings:

_____Yes _____No

Electric Shocks
If the device that provides electric shocks works correctly, the electric shocks should be no worse than unpleasant or uncomfortable. However, there is the chance that energy generated by the MRI scanner could result in you accidentally receiving shocks that are more powerful than we intend. There are procedures in place to minimize this risk.

Fear Conditioning and Extinction Task
The association between the electric shocks and the pictures to be presented during the fear conditioning and extinction paradigm might induce some anxiety when viewing the pictures in anticipation of the shock.

Unforeseeable Risks
There may be other risks and side effects that are not known at this time.

Risks of Breach of Confidentiality of Study Information
There is a possibility that if your study information were to become generally known, this knowledge of your study information could potentially impact you. Similarly, although every effort is being made to assure your confidentiality including the use of study codes instead of names and secure servers for audiotape storage and transfer, it is possible someone could without permission gain access to study related audiotapes during the time they are being used or stored for study supervision, to evaluate whether assessments carried out according to the study guidelines, and for examination of results.

Other Risks
There is also a risk of the study doctors detecting an earlier unrecognized medical or psychiatric problem. If this happens, you will be referred for appropriate treatment based on your needs and desires.

6. Can I be in the study if I am pregnant or breastfeeding?

The risks of CBD for pregnancy are not known. Therefore, because taking part in this study may harm an embryo, fetus, or breastfeeding baby, you should not become pregnant, breastfeed a baby, or father a child while participating in this study.

If you are currently pregnant, or if you are planning to start a family during the study or up to two weeks following the study, you will not be able participate in the study. You should not become pregnant while you

are participating in this study. If you are able to become pregnant, you will be required to use a medically accepted method of birth control while you participate in the study. Examples of medically accepted methods of birth control are as follows:

- Barrier methods such as condoms or a diaphragm used with spermicide (a foam, cream or gel
- that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

If you become or you think you have become pregnant during the study, you must tell the principal investigator right away and must tell your obstetrician or other health care provider caring for you during your pregnancy that you took part in this study. If you become pregnant, you will have to stop taking part in the study for safety reasons.

There is no known harm to the fetus from Magnetic Resonance Imaging. Previous use of this drug in pregnant women has shown an increased risk of cleft palate and cleft lip in unborn babies. However, since the risks have not been adequately studied and therefore are not well known, if you are pregnant, you will be asked to discontinue participation in this study and will be counseled about possible alternatives. The principal investigator may ask you to provide information about the outcome of your pregnancy and the health of your baby.

Note to Men
Because the effect of participating in this study on sperm are unknown, you will be required to use a medically accepted method of birth control while you participate in the study, using one of the methods described above.
If your partner becomes or thinks she may have become pregnant during the time you are in the study, you must tell the principal investigator right away.

7. What if new information becomes available?

During the course of this study we may find more information that could be important to you. This includes information that might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

8. What are the possible benefits of the study?

You may not benefit from taking part in this study. There is no guarantee that your symptoms will improve. You may benefit from the screening procedures that include a careful examination of your mental health condition. You may also benefit from the ongoing close mental health evaluation during the course of the study. There is a 66% (2/3) chance you will receive the active study medication CBD but it is not yet known whether or how much it will help people with anxiety and stress. We hope the knowledge gained by doing this study will help others with SAD in the future. Since there is a potential benefit to society, you may also benefit from knowing that you have contributed to the scientific understanding how CBD works through behavioral and brain mechanisms for individuals with SAD.

9. What other choices do I have if I do not participate?

You do not have to take part in this research study to be treated for anxiety. Treatment for SAD is available outside of this study. If you decide not to participate, your decision will not interfere with your future care, payment for your health care or your eligibility for health care benefits. Other treatments or procedures that are available to treat anxiety include:

- Psychotherapy, such as cognitive behavioral therapy
- Antidepressant medications, such as paroxetine or sertraline

10. Will I be paid for being in this study?

You will receive a total of $500 for taking part in this study. You will be paid $20 for the completion of in-person screening visit, $100 for baseline assessments, $120 for Visit 3 and Visit 4, $120 for day 1 of the experimental visit and $140 for day 2 of the experimental visit in the fMRI scanner. If you do not complete

the study, you will be paid for the visits you did complete. If you complete only the screening interview (which includes completing the questionnaires), you will be paid $10.

We are also able to compensate you $5.80 to cover transportation costs for each in-person assessment. In order to be reimbursed, you must give the receipts to the study staff.

As is required by the laws that apply to NYU Langone, in order for you to receive a payment (i.e. check) you need to give the study staff either your Social Security number or your Alien Registration number and will be asked to complete a IRS W9. If you do not have either of these numbers or are not willing to complete the IRS, you may be in the study but will not receive any payment.

You are required to track all payments made to you by NYU Langone for your participation in any research for this calendar year. You must let us know immediately if/when the total research payments presently equal or is likely to exceed $600.00 total (not including travel reimbursements) for this calendar year. If your total payments (for one or more studies) reach $600.00, please advise Dr. Naomi Simon at naomi.simon@nyulangone.org.

11. Will I have to pay for anything?

There will be no costs to you for participating in the research. Study funds will pay for the assessments, the CBD/placebo, and the fMRI scan.

If you need to be hospitalized due to a worsening of your anxiety symptoms, you or your insurance provider will be billed for the costs associated with this hospital stay.

You and/or your health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs or you do not have insurance, these costs will be your responsibility.

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.

12. What happens if I am injured from being in the study?

For medical emergencies contact 911. If you think you have been injured as a result of taking part in this research study, tell the principal investigator as soon as possible. The principal investigator's name and phone number are listed at the top of page 1 of this consent form.

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 for the NYU School of Medicine or Medical Center to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

13. When is the study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped or your participation ended at any time by your study clinician or the study sponsor without your consent because:

- The principal investigator feels it is necessary for your health or safety. Such an action would not

require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The study sponsor, the principal investigator, or other body responsible for monitoring the safety of the study has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Leaving the study will not interfere with your future care, payment for your health care or your eligibility for health care benefits.

14. How will you protect my confidentiality?

Your medical information is protected health information, or “PHI”, and is protected by federal and state laws, such as the Health Insurance Portability and Accountability Act, or HIPAA. This includes information in your research record as well as information in your medical record at NYU Langone Health. In compliance with NYU Langone Health policies and procedures and with HIPAA, only those individuals with a job purpose can access this information.

Medical information created by this research study may become part of your medical record. We may include your research information in your medical record for several reasons, including for the billing of services provided in connection with the study, to securely document any medical services you receive, and so that other members of the NYU Langone Health community who may treat you have access to important information about your health.

You have a right to access information in your medical record. In some cases, when necessary to protect the integrity of the research, you will not be allowed to see or copy certain information relating to the study while the study is in progress, but you will have the right to see and copy the information once the study is over in accordance with NYU Langone Health policies and applicable law.

Certificate of Confidentiality

To help us further protect your confidentiality, this research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The NIH has issued a Certificate of Confidentiality for this research. This adds special protection for the research information (data, documents, or biospecimens) that may identify you.

Research information protected by this Certificate of Confidentiality cannot be disclosed to anyone else who is not connected with the research, without your consent. With this Certificate of Confidentiality, the researchers may not disclose or use research information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, without your consent. However, disclosure, without your consent, is still necessary if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases).

The Certificate of Confidentiality cannot be used to refuse a request for information from appropriate government agencies responsible for project oversight. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your involvement in this research, including for your medical treatment. Federal regulations may also allow for the use or sharing of information for other scientific research.

15. HIPAA Authorization

As noted in the Confidentiality section above, federal law requires us, and our affiliated researchers, healthcare providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions. We are asking for your permission (authorization) to use and share your health information with others in connection with this study- in other words, for purposes of this research, including conducting and overseeing the study.

Your treatment outside of this study, payment for your health care, and your health care benefits will not be affected even if you do not authorize the use and disclosure of your information for this study.

What information may be used or shared with others in connection with this study?
All information in your research record for this study may be used and shared with those individuals listed in this section. Additionally, information in your medical record that the research team believes may be important to the study may be accessed by those listed here. This includes, for example, results from your physical examinations, laboratory tests, procedures, questionnaires, and diaries.

Who may use and share information in connection with this study?
The following individuals may use, share, or receive your information for this research study:

- The research team, including the Principal Investigator, study coordinators, and personnel responsible for the support or oversight of the study
- The study sponsors: National Institutes of Health (NIH)/ National Institutes of Mental Health (NIMH) and Ananda Scientific
- Governmental agencies responsible for research oversight, including the U.S. Food and Drug Administration (FDA)
- Health care providers, including your doctors and others who provide services to you in connection with this study, and laboratories or other individuals who analyze your health information in connection with this study.
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Data Safety Monitoring Board (DSMB), A group that oversees the data (study information) and safety of this research
- People from organizations that provide independent accreditation and oversight of hospitals and research

Your information may be re-disclosed or used for other purposes if the person who receives your information is not required by law to protect the privacy of the information.

What if I do not want to give permission to use and share my information for this study?
Signing this form is voluntary. You do not have to give us permission to use and share your information, but if you do not, you will not be able to participate in this study.

Can I change my mind and withdraw permission to use or share my information?
Yes, you may withdraw or take back your permission to use and share your health information at any time for this research study. If you withdraw your permission, we will not be able to take back information that has already been used or shared with others. To withdraw your permission, send a written notice to the principal investigator for the study noted at the top of page 1 of this form. If you withdraw your permission, you will not be able to stay in this study.

How long may my information be used or shared?
Your permission to use or share your personal health information for this study will never expire unless you withdraw it.

16. Optional permission for future use

NYULH would also like to store, use, and share your health information from this study in research databases or registries for future research conducted by NYULH or its research partners. Such health information may include biological samples from the study.

To give this additional permission, check the box below and write your initials where indicated. You may still participate in this study even if you do not give us this additional permission.

NYULH will continue to protect the confidentiality and privacy of this information as required by law and our

institutional polices. If you give this additional permission, you will continue to have the rights described in this form. You have the right to take back this additional permission at any time.

☐ Checking this box indicates my permission to store, use, and share my health information from this study in research databases or registries for future research conducted by NYULH or its research partners.

_____
Subject Initials

17. The Institutional Review Board (IRB) and how it protects you

The IRB reviews all human research studies – including this study. The IRB follows Federal Government rules and guidelines designed to protect the rights and welfare of the people taking part in the research studies. The IRB also reviews research to make sure the risks for all studies are as small as possible. The NYU IRB Office number is (212) 263-4110. The NYU School of Medicine's IRB is made up of doctors, nurses, non-scientists, and people from the community.

18. Who can I call with questions, or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on top of the page 1 of this consent form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Institutional Review Board (IRB) at (212) 263-4110.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will 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.

When you sign this form, you are agreeing to take part in this research study as described to you. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer.

Name of Subject (Print)	Signature of Subject	Date

Name of Person Obtaining Consent (Print)	Signature of Person Obtaining Consent	Date