

**University of California, San Diego
Parent Consent for Child to Act as a Research Subject**

Study Title: A Double-Blind, Crossover Trial of Cannabidiol to Treat Severe Behavior Problems in Children with Autism

Principal Investigator: Doris Trauner MD
Sponsor: The Ray and Tye Noorda Foundation

This is a research study. Research studies include voluntary subjects who choose to take part. You are being asked to let your child take part in this study because your child has autism with behavioral symptoms. Please take your time to make your decision. Discuss it with your family. Be sure to ask any questions that you may have.

Dr. Doris Trauner and her colleagues are conducting a research study to find out more about the safety and possible benefits of cannabidiol (CBD) for children with autism. There will be approximately 30 boys participating in this study at UCSD.

WHY IS THIS STUDY BEING DONE?

There are very few treatments that are effective in reducing severe behavioral problems associated with autism. These behaviors include aggressive and self-harm behaviors, frequent repetitive behaviors and severe hyperactivity. This study is being conducted to determine whether cannabidiol can reduce any or all of these problem behaviors.

This study is being done to:

- Learn if daily oral cannabidiol (CBD) is safe and tolerated in boys with severe autism
- Learn if CBD leads to a reduction in problematic behaviors (hyperactivity, self-injurious behaviors, aggression, stereotypic behaviors)
- Learn if CBD leads to other improvements in functioning in this population, including social communication, language abilities, anxiety, and sleep
- Learn more about how CBD affects the brain and brain networks

WHAT MAKES THIS DIFFERENT FROM THE USUAL TREATMENT?

This study will be administering purified CBD for research purposes to better understand its safety, as well as potential benefits, in the treatment of problem behaviors associated with autism. The oral solution of CBD that will be given to your child is called EPIDIOLEX. This is currently an approved medication for certain rare types of pediatric epilepsy. However, CBD is not an FDA approved treatment for autism at this time.

The experimental part of this study is the use of CBD. CBD is a drug that comes from the marijuana plant but does not have any psycho-active properties that are found in THC (tetrahydrocannabinol). This means that it will not cause people to get "high". The

CBD to be used in this study comes from plants and is made by GW Pharmaceuticals. It is over 98% pure CBD and contains very specific doses of CBD.

Your child may currently be receiving medications for their behavioral problems, such as psychotropic drugs. They may remain on their usual medication while they are in the study. Your child cannot use any cannabis- or hemp-derived products or treatments during their participation in this study.

If you agree to allow your child to participate in this study, the following will happen to your child:

Your child will be randomly assigned to one of two groups. One group will first receive CBD for eight weeks, and then receive a placebo (a product that looks like the drug but is not actually a drug). The other group will first receive the placebo for eight weeks, and then receive the CBD. Neither you nor the research team will know which group your child is in. All children who complete the study will receive eight weeks of CBD. This is called a crossover study design.

HOW LONG WILL YOUR CHILD BE IN THE STUDY?

Each child's participation will take between 5 and 6 months. The exact number of days that your child will be in the study will depend on scheduling availability and how many days it takes them to complete the evaluation testing.

WHAT IS INVOLVED IN THE STUDY?

Overview:

This study involves two dosing periods, each lasting 8 weeks. During one period your child will receive the CBD. During the other period they will receive placebo. No one will know which they are receiving. In between these there will be a "washout" period of four weeks. This will give time for any effect of the CBD/placebo to stop before the next dosing period starts.

The tests and procedures that will be performed during the study visits are described below. In addition to the visits listed below, the study team may ask you and your child to come in for extra visits if necessary to protect your child's well-being. This may happen if they experience some kind of negative health or behavioral symptoms during their participation in the study.

Drug Administration:

The CBD or the placebo will be given to you at the initial visit for each of the two dosing periods. It is a liquid, which is to be given two times per day. The dosing of the drug is based on your child's weight in kilograms (kg; 1 kilogram is slightly over 2 pounds). You will increase the amount of study drug weekly up to a maximum of 20 mg/kg per day with instructions provided to you by the study team during the clinical visit. During the first week your child will take 5 mg/kg per day, divided into two doses. During the second week they will take 10 mg/kg/day divided into two doses. In the third week and following that time they will take 20 mg/kg/day, divided into two doses, assuming that they do not

experience side effects that prevent the dosage increase. During the next five weeks, your child will take a constant amount of study drug that has been found to be tolerable in terms of side effects. The study team will tell you how much of the drug you should give to your child. If your child develops negative side effects Dr. Trauner may decide to lower the dose.

Research shows that CBD is absorbed into the body much better when it is taken with food, especially foods that are high in fat. Because of this you will be asked to give your child the medicine with a meal or snack, preferably one that has some fat. You will be given a diary in which you will be asked to record what, if any, food was given with the drug. We understand that in some cases it may not be possible to administer the drug with food, and that is okay.

Clinic Visits:

This study will involve frequent health check visits at the Altman Clinical and Translational Research Institute in La Jolla, CA. These visits will take approximately one hour and occur every one to two weeks. These visits will include a physical exam, electrocardiogram (brief study of heart health), vital sign testing (for example, pulse rate and blood pressure), and a blood draw. At each visit the study team will ask you questions about your child's health and discuss any concerns that you may have about side effects from the treatment.

Blood will be drawn from your child's arm during each of these visits (about 12 visits total). During each of these blood draws a total of up to 4 teaspoons of blood will be taken. Various testing will be conducted using these samples. This is described more below.

These visits will take place at baseline, and then at the conclusion of 1, 2, 4, 6, 8 weeks of each (of the two) dosing periods.

During the first visit to the clinic your child will have a urine drug screen. This is to make sure there is no THC in their system. Other drugs will not be screened for. After this your child's blood will be checked more specifically for CBD. If you believe there is any chance your child has consumed a CBD containing product in the past 4 weeks, we encourage you to wait before enrolling them. Testing positive for THC and/or CBD at the initial visit may prevent them from participating in the study, even in the future when it is no longer detectable. You will be informed of the results of your child's test, but they will not be put into their medical record.

Evaluation Visits:

This study will also involve a total of 4 more lengthy evaluations which will take place at the UCSD campus in Hillcrest, as well as an MRI center on the UCSD La Jolla campus. These evaluations are meant to better understand your child's baseline neurological functioning, and to evaluate any effects that the CBD may have. These evaluations may occur over several days if the testing cannot be completed in one day, or if your child becomes agitated or too tired from testing. Tests will include questionnaires that you

answer about your child's functioning. Your child will also undergo a variety of tests including cognitive and language tests, electroencephalogram (EEG), eye-tracking testing, and assessments of repetitive movements (stereotypies). If possible, your child will have an MRI done at each of these four evaluation time points. This will depend on their ability to stay still in the MRI machine.

Questionnaires that you or another guardian will complete:

You will be asked to complete a variety of questionnaires during each evaluation visit. These will include questions about your child's behavioral problems, other symptoms, sleep, anxiety, and other topics relating to the study outcomes of interest.

Direct Participant Testing & Evaluation:

Your child will also undergo testing during these evaluations. During these test sessions, your child will be videotaped for the entire session. Videos will later be used solely for research purposes. They will be used to analyze items such as eye contact, repetitive behaviors, social interactions, and frequency of other behaviors such as self-injurious or aggressive behaviors.

At each session there will be a period of free play. Your child will be free to explore toys and other objects in the testing room, to interact with the testers, and to allow him to become more used to the testing environment. We will also use that time to collect information about any targeted behavioral problems.

Cognitive/behavioral testing will include the observational tests to assess the severity of your child's autism. Tests of nonverbal intelligence, language abilities and visual-motor integration will also be given.

An EEG will be conducted at each evaluation timepoint. EEG is a test that examines brain waves and detects any abnormalities that may be present. This is done through electrodes which are put on the scalp and sense electrical activity within the brain. The electrodes are in the form of a cap that is designed to be similar to a baseball cap. A recording of brain wave activity will be conducted with your child awake and/or asleep.

Your child will be asked to complete some evaluations that are similar to games. These will evaluate things such as how much your child pays attention to different parts of a screen. These evaluations will take about 20 minutes total. These are not meant to diagnose or treat your child for any health conditions.

Eye tracking evaluations will be conducted by having your child wear specialized glasses. This evaluation will be done in a natural social setting. This is intended to assess any changes in social behaviors and attention.

Heart rate and heart rate variability are related to anxiety. Past research has shown that anxiety affects 40-80% of those with autism spectrum disorders. This assessment will be done by having your child wear a shirt with specially designed sensors installed, minimizing the discomfort that might occur with more traditional heart monitors. Your

child will wear the shirt during free play in the lab, and then during the testing period, to assess changes in heart rate and heart rate variability under varying circumstances.

Imaging: We may try to have your child have brain imaging done, including magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and resting state functional MRI (fMRI). These studies will be done at up to 4 time points: before dosing period 1, after dosing period 1, before dosing period 2, and after dosing period 2. We realize that this may be challenging for your child. You may bring in videos and music that your child likes if you feel that may be helpful. Scans will be done using protocols already developed by neuro-imaging experts at UCSD. Sessions will be kept as short as possible, typically no longer than 30-45 minutes. These images will provide valuable information about participants' brain structure, neuronal networks, and neurotransmitter changes. If your child is unable to lie still and quietly during the imaging procedures then they will not be completed. Completion of the imaging component is not mandatory for participation.

As a part of this study you will be asked to use an online application to record information about your child's behavior. At the time of signing this form you will be provided with a printed document that describes the terms of use and policies of the application. Please bring up any questions you may have about this document or the use of the app.

WHAT ARE MY RESPONSIBILITIES DURING THE STUDY?

During the study you will have the following responsibilities:

- Bring your child to all scheduled visits.
- Give your child the correct dose of the oral CBD or placebo solution every day, at the dosage directed by the study doctor
- Complete the daily drug diary to verify that your child has been given the appropriate dose, and return this diary to the study team when directed to do so.
- Save any unused solution and bring it back to the study site when directed by the study team
- Follow all instructions about whether your child may continue to take his regular medications or other prescribed or over-the-counter medicines during the study period.
- Tell the study team of any changes to your child's current medications, illnesses or injuries, unexpected or troublesome side effects, or problems that occur during the study. Medication updates can be provided at the next study visit after which they occur. Any significant medical developments and/or possible adverse events should be relayed to the study team. You will be provided with their direct contact information.
- Tell the study doctor if your child is going to have any elective surgery or any other medical treatment or procedure.
- Continue to make regular visits to your child's regular doctor or any other specialist doctors that your child was seeing before starting the study, since being in the study does not take the place of regular medical care.

- Make sure that the study medication is kept out of the reach of children and people who have a limited capacity to read or understand. Your child is the only person who should be given the study medication, and it should only be given in the directed dosage.
- Contact the study doctor if you have any questions about the study after you sign this form

WHAT ARE THE RISKS OF PARTICIPATING IN THIS STUDY?

Any study has risks, which may include things that could make your child sick, feel uncomfortable, or harm your child. Your child might experience side effects related to the study drug while participating in the study. All research participants in the study will be watched carefully for any side effects. However, the study team may not know all the effects that the study drug may have on your child. These side effects may be mild or serious.

Having your child take part in this study involves some risks and possible discomfort as noted below:

- The side effects that were observed in the past in studies of CBD in children include: stomach problems, low blood counts, lack of energy, tiredness, change in appetite, and changes in weight. These side effects were generally mild to moderate and were reversible upon reducing the dose or discontinuing the treatment. Your child will be monitored closely for any adverse effects of the study drug. A questionnaire about any changes in their health will be given at each clinic visit. In addition, you will be provided with contact information so that you may contact the study team at any time if concerns arise.
- **Blood samples:** Taking blood from your child's arm may cause faintness and/or swelling, pain, redness, bruising, or infection (rare) at the needle site. We can use a numbing cream on the skin (EMLA) to reduce the discomfort of the needle stick if you request this.
- **Electrocardiogram (ECG):** Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used. This is very mild.
- **Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), Functional Magnetic Resonance Imaging (fMRI):** There are no known significant risks with these imaging exams. However, your child may feel uncomfortable or claustrophobic (afraid of small spaces) because the space in the machine is small. Your child may become anxious from lying in a tight space without moving. There are also loud noises made by the machine. The scanner does not cause any pain and will not expose your child to x-ray radiation. You are able to stop the imaging scan if you would like. If your child has substantial difficulty with the scan the study team will stop the procedure.

If your child has any illness or discomfort as a result of using the study drug call your study doctor immediately. If necessary, use of the study drug may be stopped and other therapy may be started.

Other risks in this study include the following:

- ✓ Your child's condition may not improve; it may stay the same or it may worsen while participating in this study.
- ✓ There may be side effects or discomforts associated with this study, which are not yet known. There is some risk of loss of privacy. Strict protections to avoid that are described below in a section on confidentiality.

If new findings come up during the study that would affect your child's safety and/or your willingness to have your child participate in the study, you will be told as soon as possible so you can decide whether to continue or leave the study.

For more information about these risks and side effects, ask your child's study doctor.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

WHAT ARE THE ALTERNATIVES TO PARTICIPATING?

The alternative is to not allow your child to participate in this study. In this case your child will continue to receive their usual medical care. The quality of their care will not be affected.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There is no guarantee that your child will receive any benefits. However, you and your child may feel that you are benefitting in the following ways:

- Your child's condition will be checked as long as your child participates in the study. These services and evaluations should not be seen as a substitute for a careful evaluation, ongoing medical care, or follow-up by your child's regular doctor.
- You and your child may be helping others by contributing to medical research.
- The study drug may help to relieve your child's symptoms and improve his level of functioning.

The research team and institution does not benefit from the study.

CAN YOU CHOOSE TO NOT HAVE YOUR CHILD PARTICIPATE, OR WITHDRAW THEM FROM THE STUDY?

Participation in this research is entirely voluntary. You may refuse to allow your child to participate or withdraw your child at any time without penalty or loss of benefits to which you or your child are entitled. If you decide that you no longer wish your child to continue in this study, your child may be requested to come in for a final health check-in visit to ensure they are not having any negative effects and to collect any unused drug.

You and your child will be told if any important new information is found during the course of this study that may affect your wanting to continue.

CAN YOUR CHILD BE REMOVED FROM THE STUDY WITHOUT YOUR CONSENT?

Your child may be removed from the study in the event of the following:

- If they experience an adverse reaction to the drug
- If they do not follow study directions
- If the principal investigator ends the study
- If their condition worsens or changes in some way that prevents them from remaining eligible
- If they begin another medication or alternative therapy that may interfere with the results of the study, or if the dose of any medicine already being taken changes during the course of the study. All new medications or therapies, or dosage changes in ongoing medications should be reported to the study team within 7 days of any change. Substantial changes in other therapies (such as behavioral intervention) should be reviewed with the principal investigator.

WILL YOU OR YOUR CHILD BE COMPENSATED?

In compensation for you and your child's time and travel, you will receive a total of \$900 if the study visits are all completed. This is divided into \$25 payments for each of the 12 clinic visits, and \$150 for each of the four longer evaluation sessions.

ARE THERE COSTS ASSOCIATED WITH PARTICIPATING?

There will be no cost to you or your child for participating in this study. Incidental costs of participation, such as parking and gas expenses, are expected to be covered with the compensation, detailed above.

WHAT IF YOUR CHILD IS INJURED IN THE STUDY?

If your child is injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if your child is injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your child's rights as a research subject, or to report research-related problems.

WHAT ABOUT CONFIDENTIALITY?

Research records will be kept confidential to the extent allowed by law. Research records may be reviewed by the study team, the Food and Drug Administration (FDA), the UCSD Institutional Review Board and the Research Advisory Panel of California (RAPC).

Physical records containing identifiable information, such as past CBD use and medical history, are stored in locked file cabinets within a locked room in Dr. Trauner's laboratory at the Biomedical Sciences Building at UCSD, or in an interior locked room at the Center for Medicinal Cannabis Research (CMCR). Each file room has a key-card lock entry system.

Mobile data from the iPad questionnaire is HIPAA Compliant and only study staff that have been granted access rights to the data can view this information.

All blood samples are to be used for research and are not a part of any clinical care. They will be stored in a secured laboratory at the CMCR and will be labeled only with a code number. This code number can be linked back to your child only by the research staff.

Biospecimens collected from your child for this study and/or information obtained from your child's biospecimens may be used in this research or other research, and shared with other organizations. You and your child will not share in any commercial value or profit derived from the use of your child's biospecimens and/or information obtained from them.

Federal and State laws generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you or your child based on your child's genetic information. This law generally will protect you and your child in the following ways: a) Health insurance companies and group health plans may not request your child's genetic information that we get from this research. B) Health insurance companies and group health plans may not use your child's genetic information when making decisions regarding you or your child's eligibility or premiums. C) Employers with 5 or more employees may not use your child's genetic information that we get from this research when making a decision to hire, promote, or fire you or your child or when setting the terms of you or your child's employment. Be aware that these laws **do not** protect you or your child against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Under California law, we must report information about known or reasonably suspected incidents of abuse or neglect of a child including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may be required to report such information to the appropriate authorities.

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. This Web site will not include information that can identify your child.

PERMISSION FOR OPTIONAL BLOOD SAMPLE STORAGE

The impact of your and your child's contribution to research can be enhanced by permitting blood that is not used during the laboratory analyses for this specific study to be stored and utilized for future autism and CBD research. If you provide your permission, samples will be collected and stored at four timepoints. At baseline and week 8 of both dosing periods, blood that is not needed for immediate use will be stored for possible future testing. These samples may be used to isolate your child's DNA (the genetic material inside your cells). Some of these samples will be stored indefinitely for future use by the researchers of this study, or other researchers. Samples collected in the course of the study are banked and may be sent to other researchers anonymously (without identification). All samples will be identified only with a study code. If genetic or

other testing is done, results will not be disclosed to you. Only laboratory staff, trained in confidentiality and appropriate lab practices, will have access to the samples.

If you decide later that you do not want the specimens collected from your child to be used for future research, you may tell this to the study staff, who will use their best efforts to stop any additional studies. However, in some cases it may be impossible to locate and stop such future research once the materials have been shared with other researchers.

Please indicate below if you give your permission for the storage of these samples as detailed above:

_____ Please initial here if you agree to have your child’s samples collected and stored for future use.

_____ Please initial here if you DO NOT agree to have your child’s samples collected and stored for future use.

WILL I BE TOLD WHICH TREATMENT MY CHILD WAS ON?

You will not be informed of which treatment your child was on at each treatment period. The study is blinded to the investigators until it is completed. Once the study is completed, results will be analyzed and reported in the medical literature. We will provide the group results to you at that time.

WHO CAN YOU CALL IF YOU HAVE QUESTIONS?

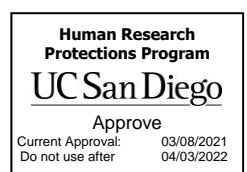
Dr. Trauner and/or _____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Dr. Trauner at 858-822-6700, dtrauner@ucsd.edu.

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

YOUR SIGNATURE AND CONSENT

Your signature below means that you have read the above information about this study and have had a chance to ask questions to help you understand what your child will do in this study and how your child’s information will be used.

You or your child can change your minds later if you want to leave the study. You will be told about any new information that may affect your child’s health, welfare, or willingness to stay in the study.



You will receive a copy of this signed and dated consent form and a copy of the “Experimental Subject’s Bill of Rights” to keep. By signing this consent form you are not giving up any of your or your child’s legal rights.

I have read this information, which is printed in English. This is a language that I read and understand. I agree to allow my child to participate.

Parent/Guardian Signature

Date

Name of Child (printed)

Age of Child

Signature of Witness (person explaining this form)

Date

SUBJECT’S BILL OF RIGHTS

It is important that the purpose and procedures of the research study are fully understood and that consent is offered willingly. A subject in a research study or someone, who is asked to give consent on behalf of another person for such participation, has the right to the following:

1. Be informed of the nature and purpose of the research.
2. Be given an explanation of all procedures to be followed and of any drug or device to be used.
3. Be given a description of any risks or discomforts, which can be reasonably expected to result from this research study.
4. Be given an explanation of any benefits, which can be reasonably expected to the subject as a result of this research study.
5. Be informed of any appropriate alternative procedures, drugs, or devices that may be advantageous and of their relative risks and discomforts.
6. Be informed of any medical treatment, which will be made available to the subject if complications should arise from this research.

Human Research Protections Program UC San Diego	
Approve	
Current Approval:	03/08/2021
Do not use after	04/03/2022

7. Be given an opportunity and encouraged to ask any questions concerning the study or the procedures involved in this research.
8. Be made aware that consent to participate in the research may be withdrawn and that participation may be discontinued at any time without affecting continuity or quality of medical care.
9. Be given a copy of the signed and dated written consent form.
10. Not be subjected to any element of force, fraud, deceit, duress, coercion, or any influence in reaching the decision to consent or to not consent to participate in the research.

If you have any further questions or concerns about your child's rights as a research subject, please contact your research doctor or the UCSD Human Research Protections Program at 858-246-HRPP (858-246-4777).