Informed Consent/Parental Permission Form
For Participation in a Research Study

STUDY TITLE: Evaluating The Neurophysiologic And Clinical Effects Of Single-Dose Baclofen, Lovastatin, Minocycline And Placebo In Fragile X Syndrome

STUDY NUMBER: 2015-8804

FUNDING ORGANIZATION: CCHMC Department of Psychiatry

Craig Erickson, M.D.
Name of Principal Investigator

513-636-4124
Telephone Number

INTRODUCTION

We are asking you to be in a research study so that we can learn new information that may help others. If you decide not to be in this study, we will still take good care of you. If you decide to be in this study, you may change your mind at any time during the study and you can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to be in the study. You can ask questions at any time.

If you are 18 years and older: This is a consent form. It explains this research study. If you decide that you want to be in this research study, then you will sign this form to show that you agree to be part of this study. If you sign this form, you will receive a signed copy of this form for your records.

If you are 15 to 17 years old: This form is also an assent form. That means that if you decide that you want to be in this research study, then you will sign this form to show that you agree to be part of this study. Your parent or guardian will also need to give their permission and sign this form for you to join the study.

Parents/Guardians: You have the option of having your child or teen join this research study. This is a parental permission form. It explains this research study. If you decide that your child can be in this study, you will sign this form to show that you agree. If you sign this form, you will receive a signed copy for your records.

The word **"you" or "I"** in this form refers to your child/teen.

WHY ARE WE DOING THIS RESEARCH?

In this research study we want to see if medication can treat excessive sensitivity to sounds which is a common and distressing symptom of Fragile X Syndrome (FXS). One medication and a placebo will be tested: baclofen. This drug has been approved by the U. S. Federal Food and Drug Administration (FDA) for the treatment of other conditions.

WHO IS IN CHARGE OF THE RESEARCH?

Dr. Craig Erickson is the researcher at Cincinnati Children's Hospital Medical Center (CCHMC) that is in charge of this study.

This study is being paid for by Cincinnati Children's Hospital Medical Center.

WHO SHOULD NOT BE IN THE STUDY

You cannot be in this study if you have any of the following:

- You are unable to take baclofen
- If you have taken any investigational drug within 3 months
- If you have a history of drug or alcohol abuse within the last 6 months.
- Any significant psychiatric or CNS neurological disease unrelated to FXS.
- If you take anticonvulsants, barbiturates, lithium and benzodiazepines
- If you have just started any psychiatric medications within the last 4 weeks
- Women who have a positive urine pregnancy test.
- After screening, you have a creatinine clearance < 50 mL/min
- If you have certain medical issues, unable to tolerate study procedures or study drug decided by the study doctor.

WHAT WILL HAPPEN IN THE STUDY?

The research staff will explain each visit to you and may give you a handout that explains each visit in more detail. You will be able to ask questions to make sure that you understand what will happen.

If you qualify and decide you want to be in the study, your study participation will last about 11 weeks and include 5 study visits. You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

These are the things that will happen to you while you are in the study:

Baseline Procedures: Visit 1

If you qualify and wish to continue, the following will be done:

- You will give a urine sample to be tested for illegal drugs.
- Women of child bearing years, you will have a pregnancy test to see if are pregnant
- You will be given several tests of your memory and concentration.
- You will have an optional blood sample drawn.
- You will have an evaluation of your fragile x symptoms.
- You will have a review of your medical history.
- You will have a medical evaluation, which includes your height, weight, head measurements, physical examination, and vision and hearing tests.
- You will have your vital signs (pulse, blood pressure, breathing rate, and temperature) checked.
- Due to the large size of the study pill, you will have the option to practice swallowing a placebo pill

- You will be randomized to study treatment (see description below)
- Your caregiver will be asked to complete questions about your behavior
  You will be given a task to test your thinking and motor skills which approximately takes 25 minutes

This baseline visit will take about 2 hours. You will return to the clinic within 60 days tobegin the single-dose phase of the study and receive your first dose of study drug

Randomization

If the researchers believe you can take part in this study, you will be assigned randomly (like pulling a number from a hat) to 1 of 2 treatment groups. Each treatment group will receive the same dose of each of the study drugs – baclofen and placebo, but the order of drugs and placebo will be different for each group. You have a 50% chance (1 in 2) of being assigned to each group. Neither you nor the researchers will be allowed to choose which group you are assigned to. Neither you nor the researchers will know which group you are in and which study drug you are taking. However, the information about your assignment can be released to you after completing all phases of the study if you wish. But, if there is an emergency, they are able to get this information.

Study Medication

If you decide to participate in this study you will be assigned to 1 of 2 treatment groups and take each of the following study drugs in different orders:

- baclofen (30 milligrams) or
- placebo

The medication and placebo will be given in 2 capsules.

Study Drug Visits: Visits 2, 3, 4, 5

After you have been randomized to your treatment group, you will begin the weekly single-dose phase. You will come to the clinic once every 2 weeks to receive a single-dose of study drug (baclofenor placebo). You will complete study procedures both before and after receiving the study drug (see description below). These 4 visits will each take about 8 hours to complete.

Pre-dose Procedures

You will be asked to come in to the clinic for each visit. The following procedures will be done:

- You will have a medical evaluation, which includes your height, weight, physical examination, motor skills, and vision and hearing tests.
- You will have your vital signs (pulse, blood pressure, breathing rate, and temperature) checked.
- You will have an optional blood sample drawn
- You will participate in an electroencephalogram (EEG) neurophysiological measures. During the EEG measures, you will wear a cap with sensors to measure the electrical activity of your brain. You will not feel these sensors working. These tests will look at how the brain functions at rest and when you are presented with visual images or sounds such as beeps or human voices. The study team will use a program to take a picture of the electrode placement on your head. This

helps the study team analyze the EEG data.

- You will watch targets and faces on a large screen while we measure and record your eye movements
- Women of child bearing years, you will have a pregnancy test to see if are pregnant.
- You and your caregiver will be asked to complete questions about your behavior
- You will be given several tasks to test your thinking skills, memory and concentration.
- These tasks require that you be seated at a table, listen and follow directions presented by the examiner, look at pictures or other testing materials, and respond to questions either verbally or by manipulating objects. The total time spent performing such tasks is approximately 35 minutes.
- You will have an evaluation of your FXS symptoms. You will be asked about current side effects.

Following the pre-dose procedures, at approximately 2 hours after you arrive, your assigned study drug for the day will be administered orally (by mouth) by a research nurse.

Post-dose Procedures

Optional blood samples will be drawn 1 to 2 hours after post dose.
Four hours after you have received the study drug:

- You have your vital signs (pulse, blood pressure, breathing rate, and temperature) checked.
- You will participate in EEG neurophysiological and eye tracking measures.
- Optional blood sampling will be 4 to 6 hours following dosing.
- You will have an evaluation of your FXS symptoms.
- You will be given several tasks to test your thinking skills, memory and concentration.
  These tasks require that you be seated at a table, listen and follow directions presented by the examiner, look at pictures or other testing materials, and respond to questions either verbally or by manipulating objects. The total time spent performing such tasks is approximately 1 hour. Frequent breaks will be offered throughout the testing session.
- You will be questioned about and examined for possible side effects of the study drug.

At the end of each visit, the study doctor will ensure that it is safe for you to leave the clinic by having your vital signs checked, asking questions about how you are feeling and by doing a physical examination.

Each of these 2 single-dose phase visits will take about 8 hours to complete. You will return to the clinic once every 2 weeks to complete these study visits.

Phone/Email Evaluation 1 Day after Single-dose Visits:
We will call or email you the day after each of your Single-dose Visits and conduct an interview. We will ask you about any side effects you may have been experiencing and about any changes in your general health. This phone call will take about 20 minutes.

Phone/Email Evaluation 1 Week after Single-dose Visits:
We will call or email you a week after each of your Single-dose Visits and conduct an interview. We will ask you about any side effects you may have been experiencing and about any changes in your general health. This phone call will take about 20 minutes.

Phone Evaluation 1 Month after Final Visit:
We will call you 4 weeks after Visit 5 and conduct a phone interview. We will ask you about any side effects you may have been experiencing and about any changes in your general health. This phone call will take about 20 minutes.

The procedures in this study are designed for research, not for medical purposes. They are not useful for finding problems or diseases. Even though the researchers are not looking at your EEG measures and other tests to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because the procedures done in this study are not for medical purposes, the research results will not be sent to you or to your regular doctor.

Clinical Report Following Study Completion:
Following the Week 10 call, the participating family will receive a report of the clinical measure scores including changes with drug/placebo treatment during each treatment period. A clinician not involved with the individual participant's clinical ratings during study will sign off on the score report provided to the participating family.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

If you agree to take part in this study, there may not be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research. We hope the information learned from this study will benefit others with FXS in the future. Information gained from this research could lead to better treatments for FXS.

You will receive a report of the clinical measures obtained throughout the different treatment periods in this study. This may be helpful by providing clinical information associated with specific study drugs.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?
Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers and your regular health care provider.

There are also risks associated with the medicine.

Baclofen is FDA approved to treat reversible spasticity associated with multiple sclerosis or spinal cord lesions. Common side effects include hypotension (low blood pressure), nausea, constipation, diarrhea, vomiting, dryness of mouth, muscle pain, muscular weakness, sedation, drowsiness, dizziness, vertigo, headache, insomnia, euphoria (intense joy), depressive state, ataxia (loss of full body control), tremor, nightmares, tinnitus (ear ringing), nystagmus (uncontrolled eye movement), visual disturbance, rash, pruritus (itching), hyperhidrosis (excessive sweating), dysuria (difficult urination), and enuresis (involuntary urination). Less common side effects are arrthymias (abnormal heart beat), dyspnea (difficult breathing), palpitations (irregular heart beat), chest pain, ankle edema, abdominal pain, anorexia, disorders of hepatic function, paresthesias (tingling), taste disturbance, dysarthia (unclear speech), syncope (loss of consciousness), dyskinesia (impaired voluntary movement), coma, urine retention, helplessness, inability to ejaculate, hematuria (blood in urine), nasal congestion, and weight gain.

Risks related to EEG Measurements:
A paste or saline is used to attach the sensors during EEG testing which may irritate the skin on the scalp or face. Irritation is mild and usually goes away quickly. Paste used on the scalp during one of the tests requires that you not use hair products on that day of testing (or it has to be washed out prior to testing), which may be inconvenient.

Risks to Fetus:
If you are part of this study while pregnant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant females cannot participate in the study. If you can become pregnant, a urine pregnancy test will be done, and it must be negative before you participate in this study. If you do become pregnant during this study, you must tell the researchers immediately Pregnancy test results will be shared with you and your legal guardian if you are younger than 18 years old.

Risks associated with blood draw
The risks of blood draw include mild discomfort, hematoma, infection, bleeding, and fainting. Standard methods and precautions will be used to protect the puncture site from bleeding and infection. To minimize the subject's anxiety and phobic reactions, we utilize Child Life personnel when needed and available. At the discretion of the nurse or the investigator, to help reduce pain at the site of the venipuncture, we will offer the use of a topical anesthetic cream or spray.

Psychological Stress
Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break or stop your participation in this study at any time.

Loss of Confidentiality
Any time information is collected; there is a potential risk for loss of confidentiality.
Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

There may be other risks that we do not know about yet.

WHAT OTHER CHOICES ARE THERE?
You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:
Besides the study drugs, there are other similar medications that you can receive outside the study in regular clinical care. Please talk to the researchers or your personal doctor about these options.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE?

Making sure that information about you remains private is important to us. To protect your privacy in this research study we will code records to remove identifiers, limit access to the study records, not using any individual identifiers in publications or reports resulting from the study.

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct

personal identifier. Your research records may be disclosed outside of Cincinnati Children's Hospital Medical Center, but in this case, they will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

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

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

The study doctor will tell you if they find out about new information from this or other studies that may affect your health, safety or willingness to stay in this study.

WILL IT COST YOU ANYTHING EXTRA TO BE IN THE RESEARCH STUDY?

Other than cost of travel to and from visits and potential time away from work for caregivers, we anticipate no other costs for subjects associated with study participation.

WILL YOU BE PAID TO BE IN THIS RESEARCH STUDY?

You will be reimbursed for your time, effort and travel while you are in this research study.

You will receive payment for this study in the form of a reloadable debit card (Clincard). We will give you a handout that will explain how to use the card. Because you are being paid for your participation, CCHMC is required by the Internal Revenue Service (IRS) to collect and use your social security number (SSN) or taxpayer identification number (TIN) to track the amount of money that we pay you. You will need to complete a Federal W-9 form for this income tax reporting. This form requires your Social Security number. This form will be given to the CCHMC business office. It will not be kept as part of your study chart. If you move, you will need to complete another W-9 with an updated address.

You will be paid $100 for each study visit as reimbursement for your time and effort.

Tissues or body fluids collected for this research may result in the development of a product that could be patented/licensed and sold. You will not be paid if this happens.

WHAT HAPPENS IF YOU ARE INJURED FROM BEING IN THIS STUDY?

If you believe that you have been injured as a result of this research you should contact the study doctor as soon as possible to discuss the concerns. Treatment for injuries is available at CCHMC. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form.

CCHMC follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact the study person

listed on page 1 of this document.
If you would like to talk to someone that is not part of the research staff or if you have general questions about your research study rights or questions, concerns, or complaints about the research, you can call the CCHMC Institutional Review Board at 513-636-8039.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?
CCHMC will need to use and share your PHI as part of this study. This PHI will come from:
- Your CCHMC medical records
- Your research records

The types of information that will be used and shared from these records include:
- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your protected health information in this study?
- Staff at all the research study sites (including CCHMC)
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the CCHMC Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?
People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?
You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?
Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your other medical care be impacted?
By signing this document you are agree to participate in this research study and give permission to CCHMC to use and share your PHI for the purpose of this research study. If you refuse to sign this document you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

Optional Blood Sampling
Pharmacokinetics, or PK sampling, Extracellular Signal Related Kinase (ERK) and Amyloid Precursor Protein (APP) are tests to measure how much study medication is in the blood (referred to as pharmacokinetics or PK sampling) and ERK/APP are molecular biomarkers found in blood. FMRP assay will be conducted to quantify the level of the fragile X mental retardation protein in cells. Blood samples may be drawn 3 times, at pre-dose, 1-2 hours and 4-6 hours after on each day that study drug is given and once at baseline for ERK/APP, and FMRP. The blood tests are optional and not required for participation.

_____ Yes, I agree to have Pk ERK/APP, and FMRP blood samples drawn

_____ No, I do NOT agree to have Pk ERK/APP, and FMRP samples drawn

SIGNATURES

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research you will document your consent by signature below.

You will receive a copy of this signed document for your records.

_____
Printed Name of Research Participant

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_____ _____
If research participant is 18 years and older Date
Signature of Research Participant Indicating Consent

_____ _____
If research participant is 15-17 years and older Date
Signature of Research Participant Indicating Assent
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If research participant is younger than 18 years or caregiver:

_____
Printed Name of Legally Authorized Representative (Parent or Guardian)

_____ _____
Signature of Legally Authorized Representative Date

_____
If signed by a Legally Authorized Representative, a description of such representative's authority must be provided

_____ _____
Signature of Individual Obtaining Consent Date