Final Informed Consent Document

for

Distinct Mechanisms of Cognitive Behavioral Therapy Effects in Youth with Migraine: Insights from Neuroimaging and Quantitative Sensory Testing *(AKA: The How and Why Youth with Headaches Get Better Study) (R01NS101321)*

&

Dissecting Neural Mechanisms Supporting Mind and Body Approaches to Pain Reduction in Youth with Migraine (*R01AT010171)*

Short Title: CAP Imaging Study 2

NCT# 03472092

Title of research study: *Distinct Mechanisms Of Cognitive Behavioral Therapy Effects In Youth With Migraine: Insights From Neuroimaging And Quantitative Sensory Testing: The How And Why Youth With Migraines Get Better (NINDS)/Dissecting Neural Mechanisms Supporting Mind and Body Approaches to Pain Reduction in Youth with Migraine (NCCIH) (CAP Imaging Study)*

Investigator: **Scott W. Powers, PhD and Robert Coghill, PhD**

Contact Info: **513-636-8106 or 513-374-7437**

IRB Protocol #: **2019-0973**

Drug Name: **Amitriptyline**

Funding: **National Institute of Neurological Disorders and Stroke (NINDS) & National Center for Complementary and Integrative Health (NCCIH)**

Key Information:

The following is a short summary of this study to help you decide whether to be a participant in it. More detailed information about the study is listed later in this form. This document does not replace the discussion you should have with the research team about this study including having any questions or concerns answered.

Parental Permission/Assent: If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this form, we mean you or your child; "we" means the study doctor and other staff.

Reason for the study:

We are inviting your child to participate in this research because your child is between the ages of 10-17 and has migraines. The purpose for this research study is to learn more about whether changes in brain activity are related to differences in the way people feel pain both before and after receiving one of five different interventions [one of 3 behavioral therapies (A, B, or C), a placebo pill, or amitriptyline]. All three behavioral therapies (A, B, and C) provide your child with skills to better manage pain. The results of this study can help us understand how headache pain varies between people and lead to better treatments for children with headaches.

Procedures:

Your child will be enrolled in this study for a total of 6 months. During the first 4 weeks, your child will be asked to keep a daily headache diary. During this time, your child will also complete some questionnaires, have an ECG, an MRI, and undergo sensory testing using pressure and temperature stimuli. If your child can participate in this study, they will receive one of five different interventions (one of three behavioral therapies, a placebo pill, or Amitriptyline). Their intervention will last for 8 weeks. Once your child completes their intervention, they will repeat the questionnaires, MRI, and sensory testing. During this study, they will attend a total of 5 study visits (plus 6-8 more if they are assigned to one of the behavioral therapies) followed by a safety phone call 4 weeks later. They will complete online questionnaires 3 months after the final study visit.

More detailed information about the study procedures can be found under ***"(Detailed Procedures)"***

Who should not be in this study:

Your child cannot be in this study if he/she has any of the following: is uncomfortable in tight spaces (claustrophobic); has electronic devices inside his/her body, orthodontic braces or other metallic implants that would interfere with the MRI; is pregnant; or has a medical diagnosis that your child's neurologist believes would interfere with participating in the study.

Your child cannot be in the study if he/she is currently use any prescriptive or over the counter medications unless being used for the treatment of allergy or asthma, ADHD, or anxiety/depression. Your child cannot be currently using any of the following medications/products: headache prevention medication (e.g. Amitriptyline, Topiramate).Your child also cannot be in the study unless he/she agrees to limit the use of non-specific acute medication, such as NSAIDS (e.g., Ibuprofen), to no more than 3 times per week, or headache specific acute medications, such as triptans, [e.g. Almotriptan (Axert), Eletriptan (Relpax), Frovatriptan (Frova), Naratriptan (Amerge), Rizatriptan (Maxalt), Sumatriptan (Imitrex), Treximet, Zolmitriptan (Zomig)] to no more than 6 times per month while enrolled in the study.

Risks to Participate:
Being in this study involves some risks. You should discuss the risk of being in the study with the study staff. The table below shows the most common and most serious side effects that researchers know about. We do not know all of the side effects that may occur.

COMMON, SOME MAY BE SERIOUS	
Amitriptyline:	Amitriptyline can have some side effects such as dry mouth, sleepiness, dizziness, heartbeat changes, or lowered blood pressure. These side effects are usually uncommon (for example, occur in less than 10% of patients).

More detailed information about the risks of this study can be found under ***"(Detailed Risks)"***

Benefits to Participate:
Being in this study may not help your child right now. However, when we finish the study, we hope that we will know how behavioral therapies (A, B, or C), placebo, or amitriptyline might help other children with headaches.

Other Options:
Participation in research is completely voluntary. Your decision to participate or not to participate will not affect the care your child receives.

Cost to Participate:
There are not costs associated with study participation. Neither you nor your child's insurance company will be billed for anything related to this study.

Payment:
If you agree to take part in this research study, we will pay you (your child) for his/her time, effort, and travel while your child is in this research study. You (your child) will only receive payment for study visits that are completed. You (your child) will receive $255 for visits associated with the screening phase. He/she will receive $335 during the intervention phase for completing the randomization visit, safety visit, and final visit. If your child is randomized to one of the behavioral groups (A, B, or C), you (your child) will receive an additional $160 for the 8 sessions he/she will complete with a psychologist. After completing the follow up phase (online questionnaires) you (your child) will receive $20. A total of $610 ($770 for the behavioral groups A, B, or C) will be provided for your (your child's) time and effort if he/she completes each of the study visits.

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

Additional Study Information:
The following is more detailed information about this study in addition to the Key Information.

If I have Questions or would like to know about:

Who to talk to…	**You can call …**	**At …**
• Emergencies • General study questions • Research-related injuries • Any research concerns or complaints	**PI Name:** Dr. Scott Powers or Dr. Robert Coghill	**Phone:** 513-636-8106 or 513-374-7437
• Emergencies • General study questions • Research-related injuries • Any research concerns or complaints	**Lead Study Coordinator**	**Phone:** 513-636-1840
• Your child's rights as a research participant	**Institutional Review Board** This is a group of scientists and community members who make sure research meets legal and ethical standards.	**Phone:** 513 636-8039

Detailed Procedures:
This study will have 3 Phases (Baseline Screening, Intervention, and Follow Up). Each phase takes a different amount of time.

The Screening Phase is first, it will last for about 4 weeks. After agreeing to participate in the study, your child will be taught how to fill out a headache diary. Your child will be asked to keep a screening headache diary. During Screening your child will fill-in a daily calendar by recording the occurrence of headaches/migraines, how long they last in hours, and how severe the pain is. Your child will not take any migraine prevention medication during this time. We will obtain a medical history about your child's headaches. He/she will also complete some questionnaires. These questionnaires ask about your child's demographics (name, address, phone number, email, parent/guardian contact information, ethnicity, gender and race), and how much headaches affect his/her day to day activities at school, home, play, and socially. The questionnaires will also ask questions about whether your child is having any difficulty doing regular activities (such as chores, homework, watching TV, and sleep). Some of the questions are about how you and your child feel from day to day. Your child will have an electrocardiogram (ECG) to measure the rhythm of his/her heart. For girls who participate in the study, a urine sample will be collected to test for pregnancy at 4 visits throughout the study (screening, randomization, the safety visit, and the final endpoint visit). Positive pregnancy test results will be told to both you (parent/guardian) and your child.

During the MRI scan your child will be in a cylindrical machine for about an hour. Cushions will be used to hold your child's head still during the scans. When your child is comfortably situated in the MRI scanner, he/she will have a series of scans to look at brain activity. Each series of scans takes several minutes, and there will be a rest period of a few minutes between scans. Your child will also receive scans looking at brain structure. It is important for the study for your child to be comfortable in the scanner. If he/she is not comfortable, we will ask him/her to let us know and we can stop or try to make him/her more comfortable. The MRI technologists will be only a few feet away and will be in constant communication via an intercom system. During the MRI your child will be required to turn his/her cell phone off and to not have any family/friends in the room during testing.

Your child will also undergo sensory testing using pressure and temperature stimuli. A pressure device will be placed against your child's forearm before and during immersion of his/her hand or foot into a cold-water bath. The procedure will also be repeated at his/her shoulder. Your child's foot or hand may begin to ache while in the water. Using a temperature-controlled water bath, he/she will be asked to rate his/her pain or discomfort using a pain rating scale. The cold and pressure used during the test are chosen so that most people can tolerate them. None of the pain stimuli are damaging to the body. This test also lasts about 1 hour. For all of these procedures, your child can stop the procedures either by **removing his/her hand or foot** or **simply saying stop** at any time so that he/she does not experience pain he/she finds unacceptable.

Your child will be asked to wear an activity measurement device which looks like a watch, on your wrist. This device measures the amount and intensity of movement and light. The device also provides information about your child's sleep, which could be related to pain. Your child will wear the watch for one week prior to the randomization visit. In addition to the watch, your child will be asked to complete a Daily Diary. Your child will be sent home with

a diary to complete each day for up to a week. The diary includes questions about sleep and symptoms your child might have felt during the day. This diary needs to be completed in the morning after waking up and in the evening before going to bed. It takes approximately 5 minutes to complete.

If your child is eligible to be in the study, he/she will be "randomized" into one of 5 intervention groups. Being randomized means your child will be put into an intervention group by chance, like flipping a coin. Your child will have a 1 in 5 chance of being in any one intervention group. If your child is assigned to the placebo pill or amitriptyline group, we will not tell you or your child which pill your child is taking until your child finishes the study. Neither you, your child, nor your study doctor will know which intervention has been chosen by chance for your child. But, if there is an emergency, they are able to get this information.

The Intervention Phase is the second phase; it will last for about 12 weeks. During this phase, your child will receive one of the five interventions [Behavioral Treatment A, B, or C, a placebo pill, or amitriptyline] for 8 weeks followed by a safety phone call 4 weeks later.

A computer program will put your child into an intervention group by chance. Your child will have a one in five chance of being in each group. Neither you, nor your child, or the study doctor or study staff can choose your child's intervention group and will not know which one of the interventions your child is receiving.

If your child is in Behavioral Group A, your child will meet with a psychologist for a total of 8 sessions. These sessions each last about 45 minutes and focus on mind and body techniques that will teach your child ways to use relaxation and cognitive coping skills to manage pain. During 3 of those sessions you may be asked to attend the session to learn ways to coach your child. About half of the 8 sessions will be done at Cincinnati Children's Main Campus and the remaining sessions will be offered via telehealth (Skype or phone). How we offer these sessions (at Cincinnati Children's Main Campus or using telehealth) can be adjusted to meet the needs of your child and your family. Between each session, your child will be asked to practice some of the skills that were taught.

If your child is in the Behavioral Group B, your child will meet with a psychologist for a total of 8 sessions. These sessions each last about 45 minutes and focus specifically on mind and body techniques such as deep breathing and muscle relaxation skills to manage pain. During 3 of those sessions you may be asked to attend the session to learn ways to coach your child. About half of the 8 sessions will be done at Cincinnati Children's Main Campus and the remaining sessions will be offered via telehealth (Skype or phone). How we offer these sessions (at Cincinnati Children's Main Campus or using telehealth) can be adjusted to meet the needs of your child and your family. Between each session, your will be asked to practice the some of the skills that were taught.

If you are in the Behavioral Group C, your child will meet with a psychologist for a total of 8 sessions. These sessions each last about 45 minutes and teach the use of tests of evidence and other cognitive strategies such as positive coping statements and pleasant activities and mindfulness to manage pain. During 3 of those sessions you may be asked to attend the session to learn ways to coach your child. About half of the 8 sessions will

be done at Cincinnati Children's Main Campus and the remaining sessions will be offered via telehealth (Skype or phone). How we offer these sessions (at Cincinnati Children's Main Campus or using telehealth) can be adjusted to meet the needs of your child and your family. Between each session, your will be asked to practice the some of the skills that were taught.

*If your child is in the Placebo Pill **or** Amitriptyline Pill Group,* we will give him/her the study drug and tell him/her how to take it.

Your child will also track his/her headaches daily on a headache diary during the Intervention Phase. To monitor how your child feels, we will have him/her come in for a medical check-in visit with the study staff. This visit will occur about a month after your child starts his/her intervention. After your child has been receiving his/her intervention for about 8 weeks, your child will come back for a final study visit where he/she will repeat the questionnaires, MRI, and sensory testing that he/she completed during the screening phase. At this point, your child will not continue to keep a daily headache diary. Your child will be contacted again about a month later to answer a few questions about how he/she is feeling.

The Follow Up Phase is the final phase of the study. Your child will be contacted about 3 months after the final study visit and be asked to complete an online set of questionnaires. These questionnaires will take about 20-30 minutes to complete. These questionnaires will ask about your child's headaches, medicine use, healthy habits, illnesses, quality of life, pain, and sleep. If your child does not have access to a computer, he/she can complete these questions on paper and mail them back to us.

Change of Mind/Study Withdrawal:
You can leave the research at any time; it will not be held against you. We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

Detailed Risks:

LESS COMMON, LESS SERIOUS	
Questionnaires	Some questions asked may make your child uncomfortable or cause your child to remember a situation that was upsetting. Your child does not need to answer any questions he/she does not wish to answer and he/she can stop at any time. If your child becomes very upset during the testing at any time, we will end the testing. We will also offer to have your child speak to someone about what they are feeling.
MRI Scanning	The MRI scan is not associated with any known risks to adults or children, but may be uncomfortable because your child will be lying in a small space. If your child cannot tolerate this, the scan will be stopped immediately. During scanning, the MRI machine produces loud noises, so his/her ears will be protected

	by plugs or specialized headphones. Persons with any electronic objects or certain metal objects in their head or body may not participate because these objects may malfunction, heat up, or move. Other objects, like braces and permanent retainers, can cause a lot of problems with the MRI images. A checklist of excluded metal objects will be presented to you by the MRI technician or study staff prior to the MRI scan. If your child is a girl, we will require a negative pregnancy test before conducting a MRI. Any female with a positive pregnancy test will be excluded from having a scan.
Sensory Testing	The testing uses water at temperatures similar to what we experience during daily activities (e.g. snow, ice water bath, handwashing, dishwashing, etc.). The sensation of putting your child's hand or foot in the water will produce pain sensation, but the risk to your child is minimal, because the pain is short lived, and generally goes away immediately after the test. However, the pressure stimulus may cause mild transient bruising of the skin in some people for up to several hours, but does not cause any damage to the body. During the testing, your child can easily pull away from the water bath or pressure device and stop stimulation at any time. If your child becomes very upset during the testing at any time, we will end the testing.
Activity Device	The device looks like and is the size of a large wristwatch, and if your child is not used to wearing a watch, it might be uncomfortable. Your child may wear it on the other arm from where he/she wears his/her wristwatch. If your child's skin becomes irritated, your child may discontinue wearing the device, but we will still ask your child to complete the Sleep Diary.

Pill Based Treatments (Placebo Pill or Amitriptyline)	The placebo pill or active study drug (Amitriptyline) may not help your child feel better or prevent your headaches. Your child may also get side effects from the pills given in this study. Most side effects do not last long but sometimes they can be serious. Side effects for the placebo pill and amitriptyline that are used in this study are listed below: The placebo pill is commonly called a sugar pill. There are no known risks associated with taking the placebo. Amitriptyline can have some side effects such as dry mouth, abdominal pain, bitter taste, sleepiness, dizziness, heartbeat changes, or lowered blood pressure. These side effects are usually uncommon (for example, occur in less than 10% of patients). These side effects are usually mild and are reversible. More serious side-effects are heart rhythm changes (cardiac dysrhythmia), increased blood pressure, fainting, and a decrease in red and white blood cells. Rare side-effects include: unusual heart beat pattern, heart attack, blood cell or blood vessel changes, decreased liver function or jaundice, seizure, suicidal thoughts, or suicide. The study staff will carefully monitor any side effects that your child may have through the regular monthly check-up visits as described earlier. The study doctor will be able to reduce/stop the medicine if necessary. If there are any side effects during the study, the safety monitoring committee for this study will need to be informed. Tell the study staff right away if your child has any of these side effects. Please tell them if your child has any other problems with his/her health or the way he/she feels during the study. Could your child have an allergic reaction if he/she takes the study medication? Sometimes people have allergic reactions to drugs. Let the study staff know if your child has allergies, asthma, or nasal polyps. If you have a very bad allergic reaction, your child could die. Some things that happen during an allergic reaction are: ▪ a rash ▪ having a hard time breathing or wheezing when you breathe ▪ sudden drop in blood pressure (fainting) ▪ swelling around the mouth, throat, or eyes

	▪ fast pulse (fast heart beat) ▪ sweating Your child should get medical help and notify the study staff if he/she experiences any of these or any other side effects during the study. When taking any new medication, your child should be careful and not drive, operate machinery, or engage in other activities where you are required to be wide awake until he/she knows how the medication will affect him/her.
Online Follow Up Questionnaires	These questions should not result in any distress. It is a web-based group of questions that your child can take at his/her own pace. Your child may become frustrated if he/she is asked questions that he/she does not know how to answer. All study participants are going to be asked the same questions. Your child will be told at the beginning of the study and reminded during the study that he/she does not need to answer any questions that he/she does not wish to answer and that your child can stop answering the questions at any time. In addition to the risks or discomforts listed here, there may be other risks that are currently not known. Also, the risks or discomforts described here may occur more often or be more severe than have been seen before. There is also a risk that the interventions tested in this study will not work as well as your child's current or other standard treatment. There may be medical risks if your child stops his/her current treatment in order to be in this study. Ask the researcher about these risks.

Privacy:
Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete privacy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization.

Samples and/or data collected for or generated from this study could be shared and used for future research. Samples and /or data may be shared with other collaborators at Cincinnati Children's and possibly with outside collaborators, who may be at another institution or for-profit company. If your child is assigned to a behavioral therapy group, each session will be audio recorded and only the study team will have access to the

recordings to make sure the treatments are being delivered properly. All recordings will be destroyed every 12 months once they have been reviewed and rated.

If information that could identify your child is removed from your child's information or samples collected during this research, that information or those samples could be stored and used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

If injured while in the study:
If you believe that you have been injured as a result of this research, you should contact the Dr. Scott Powers or Dr. Robert Coghill as soon as possible to discuss the concerns. Treatment for injuries is available at Cincinnati Children's. 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.

Cincinnati Children's 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.

Return of results:
Most tests done or images obtained in research studies are only for research and have no clear meaning for healthcare. If the research with your information gives results that do have meaning for your health, the researchers will contact you and ask you if you would like to know what they have found. You can say No to hearing about the results at that time if you desire. If the researchers return results to you, it may be because they think you could have a health risk and want to recommend that the test should be re-done to check the results. If this happens, then you may want to get a second test or consult your own doctor. You may have to pay for those additional services yourself.

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?
Cincinnati Children's Hospital Medical Center (Cincinnati Children's) will need to use and share your PHI as part of this study. This PHI will come from:

- Your Cincinnati Children's 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 Cincinnati Children's)
- 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 Cincinnati Children's 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.

Will your child's other medical care be impacted?

By signing this document, you / your child agree to participate in this research study and give permission to Cincinnati Children's to use and share you/your child's PHI for the purpose of this research study. If you refuse to sign this document, you/your child will not be able to participate in the study. However, you/your child's rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

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/your child should participate in this research, you will document your permission by signature below.

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

_____
Printed Name of Research Participant

_____ _____
Signature of Research Participant Indicating Consent or Assent Date

_____ _____
Signature of Parent or 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