USING FMRI TO UNDERSTAND RESPONSE TO AN INTEGRATIVE TREATMENT FOR PAIN AND ANXIETY IN PEDIATRIC FUNCTIONAL ABDOMINAL PAIN DISORDERS (FAPD)

Principal Investigator:

Natoshia Cunningham, PhD
Assistant Professor of Family Medicine
College of Human Medicine
Michigan State University

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Revision History

Version Number: 1
Version Date: 12/7/18

Version Number: 2
Version Date: 3/22/18
Summary of Revisions Made: A detailed procedure for monitoring and recording adverse events and severe adverse events was added. The number of assessment visits for each time point (baseline and post assessment) has been changed from 2 to 1. The protocol was revised so that the CDI will be administered at screening so that all eligibility criteria are met by participants prior to starting the baseline assessment. The protocol also now states that the PI of the study will be blind to group assignment and Dr. Kashikar-Zuck will provide clinical supervision. A table about blinding and additional explanatory text was added. The randomization procedures were changed. Lastly, measures including the adverse event query form, menstruation query form, Parent Pain Visual Analog Scale, and Concomitant Medications Form were added to the table of events and the Anxiety Diagnostic Interview Schedule was removed.

Version Number: 3
Version Date: 4/30/18
Summary of Revisions Made: The protocol was revised so that the Functional Disability Inventory (FDI) and Visual Analog Scale for Pain Intensity (VAS) will be administered at the screening visit in addition to the baseline and post assessment visits. Additional eligibility requirements were included in the inclusion criteria including at least moderate disability (FDI $\geq$ 8) and a highest reported pain of at least 3/10 in the past 2 weeks according to the VAS. Additionally, participants and their parents will have the option to complete baseline and follow up assessment measures at home prior to their scheduled visit using their own electronic devices. We will provide them with a RedCap link to the measures via email within a few days of their scheduled visit. This option would reduce the length of the in-person assessment visits and thus reduce participant burden. If participants do not choose to complete measures prior to their visit, they will be administered during the assessment visit. Text detailing this was added to the protocol. The number of participants we plan to approach was also adjusted for accuracy.

Version Number: 4
Version Date: 5/15/18
Summary of Revisions Made: The protocol reformatted to comply with the NCCIH protocol guidelines.

Version Number: 5
Version Date: 8/15/18
Summary of Revisions Made: The screening procedures were amended such that in circumstances in which the FDI, SCARED, or Numeric Rating Scale (NRS) are unavailable in

EPIC, any participant approached will be consented and administered all three measures. We have noted that if the scores from the three measures indicate study ineligibility, the remaining screening measures will not be given. Moreover, the protocol now allows for anyone interested in the study who was unable to meet in-person with study staff during their outpatient visit to set up a screening appointment outside of an office visit. FAPD will be confirmed with the provider using the EMR and/or direct communication with the provider. Abdominal migraine was added to the description of the Rome IV FAPD Diagnosis Checklist. The explanation of the water load symptom provocation task (WL-SPT) was revised to state that the WL-SPT has been used in adult studies. The protocol now states that the Adverse Event Query Form will be administered during ADAPT session 2 and post-assessment for participants randomized to the ADAPT treatment group. The protocol was also revised to explain that participants randomized to the waitlist will receive the Adverse Event Query Form at post-assessment, and if they choose to participate in ADAPT after the waitlist period, they will receive the Query during ADAPT session 2 and over the phone after ADAPT session 6. We have clarified that the Numeric Rating Scale (NRS) will be used for screening, while the baseline and post-assessments will primarily use the Visual Analog Scale (VAS). If the VAS cannot be obtained because of technical difficulties with the slider, we will use the NRS instead. The protocol now explains that we will allow up to 8 weeks to complete ADAPT, rather than 6 weeks. Several typographical errors were corrected, including in sections 6.2.3, 6.2.4, 7.2, 7.3, and 11.2. We also updated the Menstruation Query, Concomitant Medications, and Baseline/Post Demographic Information forms to include clarifying questions and language. For the Baseline/Post Demographic Information Forms under the "School Information" section, "Not Applicable" responses were added to increase clarity. The Menstruation Query for baseline and post assessment were revised to include a question about current pain levels due to menstruation. The FDI-Child and FDI-Parent Forms had item 8 modified to increase clarity for participants and caregivers whose children are not currently in school. The fMRI Pain and Anxiety Ratings Form was updated to add a clarifying "not applicable" option to an item along with a notes section to explain any unusual circumstances such as the need to conduct a fMRI rescan due to significant participant movement. Updated version numbers were added to revised measures. An "Other Pain" measure was added to assess alternative pain sources and better contextualize imaging data. This measure will be administered during baseline and post assessment. The Contact Information form was modified to allow for more clarifying information. The Adverse Event Query, Adverse Event Detail, and Serious Adverse Event forms have also been updated to reflect more accurate administration time points (ADAPT Sessions 2 and 6, Post Assessment).

Version Number: 6
Version Date: 08/04/2020
Summary of Revisions Made: The protocol has been revised in response to the PI's change in institution. At the present site—Michigan State University (MSU)—the study team will collaborate with Helen DeVos Children's Hospital (HDVCH)/Spectrum Health (SH). Participants will be recruited from pediatric GI clinics at HDVCH and the fMRI portion of the study will be conducted at SH. The study team roster has been updated to reflect the change in research staff. We anticipate actively enrolling participants over the next two years, though the anticipated number of participants to enroll and complete the study have not been changed. The

inclusion criteria have been adjusted to no longer include greater than minimal levels of disability and pain as requirements to qualify for the study. During our initial launch of the study we found that pain levels and pain-related disability at the time of recruitment were not generally reflective of pain levels at the time of neuroimaging. Therefore, discounting participants due to current pain levels at the time of their GI visit seemed unnecessary. Further, we removed the criterion regarding disability levels, as disability levels widely fluctuate in this population and are not an outcome of this study. The method of reimbursement has changed, though the amount has not been altered. A few COVID-19 related modifications have also been made: Recruitment can occur virtually. Secondly, participants will now complete all ADAPT sessions virtually, using a HIPAA compliant videoconference platform or phone. Measures of parent and child COVID-related distress have been added to the study. Finally, the ACEs caregiver measure has been added to the baseline and post-assessments of the study.

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STUDY TEAM ROSTER

Natoshia Cunningham, PhD
Assistant Professor of Family Medicine
College of Human Medicine
Michigan State University
15 Michigan St NE
Grand Rapids, MI 49503
natoshia@msu.edu
(616) 234-2821

Brittany Barber Garcia, PhD
Pediatric Psychologist
Pediatric Behavioral Health
Helen DeVos Children's Hospital
35 Michigan St NE
Grand Rapids, MI 49503
Brittany.BarberGarcia@helendevoschildrens.org
(616) 267-2830

David Zhu, PhD
Professor of Radiology, Psychology, Electrical & Computer Engineering and Biomedical Engineering
Michigan State University
846 Service Rd
East Lansing, MI 48824
zhuda@msu.edu
(517) 884-3345

Judith Arnetz, PhD, MPH, PT
Professor; Associate Chair for Research, Director of Faculty Development in Research
College of Human Medicine
Michigan State University
15 Michigan St NE
Grand Rapids, MI 49503
arnetzju@msu.edu
(517) 884-0436

Mathew Reeves, PhD
Professor of Epidemiology and Biostatistics
Michigan State University
909 Wilson Rd
East Lansing, MI 48824
reevesm@msu.edu
(517) 353-8623

PARTICIPATING STUDY SITE

Natoshia Cunningham, PhD
Michigan State University
Department of Family Medicine
15 Michigan Street NE
Grand Rapids, MI 49503
(616)243-2821

STUDY MEMBER EXPERTISE

Staff Member	Role	Demonstrated Qualifications
Dr. Natoshia Cunningham	Candidate/PI	-Research faculty in the department of family medicine -Licensed clinical psychologist -Research: Assessment and treatment of pediatric pain and anxiety; Neuroimaging to understanding pain and tx response
Dr. David Zhu	Co-Primary Mentor (Neuroimaging)	-Director and MR physicist, MSU Cognitive Imaging Research Center -24 years MRI research experience -15 years neuroimaging experience with multidisciplinary teams (including psychologists and neuroscientists)
Dr. Judy Arnetz	Co-Primary Mentor (Health systems research)	-Associate Chair for Research in MSU's Department of Family Medicine (where PI is housed) -Health systems research expertise (i.e., examining organizational determinants of healthcare safety)
Dr. Brittany Barber Garcia	Consultant (Primary Interventionist)	-Licensed clinical psychologist -Specialty in pediatric pain management
Dr. Mathew Reeves	Consultant (Statistical Analysis)	-Statistical analysis for clinical trials & health outcomes research in individuals with chronic conditions

PRÉCIS

Study Title

Using fMRI to understand response to an integrative treatment for pain and anxiety in pediatric functional abdominal pain disorders (FAPD).

Objectives

Aim 1. Left AMY-PFC functional connectivity will be significantly diminished (i.e., evidence of decreased hyperconnectivity) during the water load symptom provocation task (WL-SPT) post ADAPT vs. waitlist.
Aim 2. Brain activations associated with cognitive (PFC), affective (pgACC, AMY), and visceral afferent (INS, thalamus, aMCC, S1 & S2) pain will significantly be more diminished after ADAPT vs. waitlist.
Exploratory Aim. Changes in functional connectivity and brain activations following ADAPT will correspond to reductions in pain (intensity and unpleasantness) and anxiety ratings.

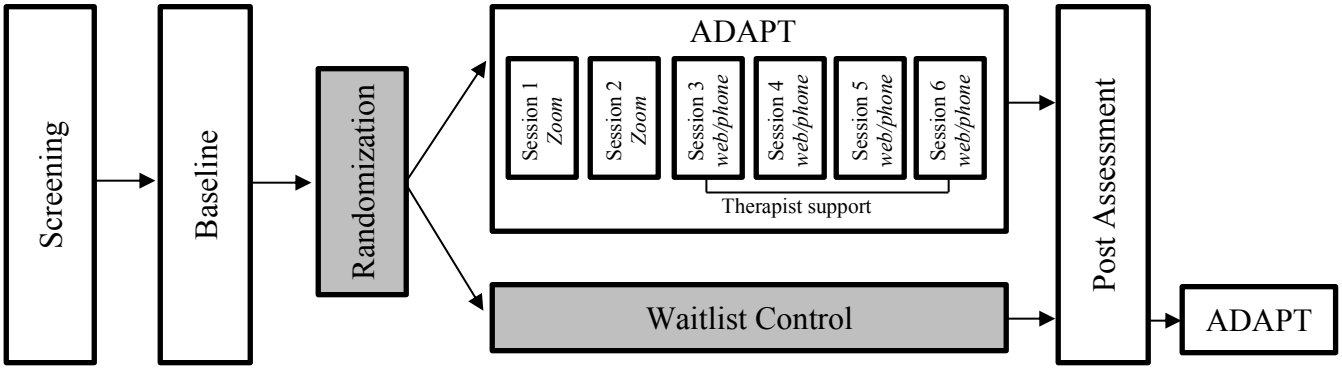
Design and Outcomes

In this study, brain mechanisms implicated in the modulation of pain during a symptom provocation task in relation to response to a psychological intervention for pediatric FAPD will be investigated. Participants with FAPD and comorbid anxiety will complete a screening to assess eligibility. Next, they will complete a baseline assessment where they will undergo an fMRI to explore changes in functional connectivity during visceral pain induction (via the water load symptom provocation task; WL-SPT). Participants will then be randomized to either ADAPT or waitlist control. A post assessment will be conducted approximately 6 weeks later where participants will again undergo an fMRI and complete the WL-SPT. Changes in functional connectivity and brain activations will be observed and compared for participants in each treatment condition (ADAPT intervention or waitlist control).

It is expected that Left AMY-PFC functional connectivity will be significantly diminished (i.e., show evidence of decreased hyperconnectivity) during the WL-SPT post ADAPT vs. waitlist (Aim 1). In addition (Aim 2), brain activations associated with cognitive (PFC), affective (pgACC, AMY), and visceral afferent (INS, thalamus, aMCC, S1 & S2) pain will significantly be more diminished after ADAPT vs. waitlist. Finally, we predict changes in functional connectivity and brain activations following ADAPT will correspond to reductions in pain (intensity and unpleasantness) and anxiety ratings (exploratory Aim).

Conventional blood oxygenation level dependent (BOLD) fMRI will be used to assess functional connectivity to capture moment-to-moment fluctuations in activity (Aim 1). In Aim 2, changes in regional brain activation for those receiving ADAPT will be compared to those in the waitlist condition. The novel arterial spin label (ASL) MRI technique will be used to gain inferences into regional brain activity since these activations represent a relatively steady-state. In line with the NCCIH funding priorities, this study seeks to increase understanding of the mechanisms through which mind and body approaches impact clinical outcomes in chronic pain and

anxiety. Results will advance the field by providing crucial information needed for the refinement and testing of a tailored mind body intervention for FAPD and comorbid anxiety.



Interventions and Duration

In this study, a psychological intervention, Aim to Decrease Anxiety and Pain Treatment (ADAPT), was developed and will integrate mindfulness meditation with cognitive behavioral therapy approaches for managing pain and anxiety to improve patient outcomes. ADAPT is a remotely delivered individual therapy with caregiver involvement that consists of 2 video-recorded sessions with an interventionist (60 minutes) once per week for the first two weeks, followed by 4 weeks of self-paced web modules (45 minutes per week) in conjunction with interventionist support (15 minutes per week). Of note, participants will complete the ADAPT program through a HIPAA compliant video platform (Zoom) or over phone calls as an alternate delivery method. Zoom sessions will be video recorded to measure interventionist adherence and for training purposes. The duration of ADAPT is 6 weeks, although up to eight weeks will be permitted to account for scheduling conflicts and participant illness. Preliminary testing has shown that ADAPT successfully reduces pain and anxiety over time.

Participants randomized to ADAPT will be actively involved in the study for a ~10 week period (from screening to post assessment). Those who are randomized to the waitlist control and then opt to receive ADAPT afterwards will be involved for ~16 weeks.

Sample Size and Population

The target population is male and female youth between the ages of 11-16 with functional abdominal pain disorders (FAPD) and clinically significant anxiety. Youth will be recruited from pediatric gastroenterology clinics at Helen DeVos Children's Hospital. We aim to have between 17 – 25 participants in each arm for a total N of 34 - 50 participants in the study. Gender and age will be used as blocking variables in randomization.

1. STUDY OBJECTIVES

1.1 Primary Objective

Left AMY-PFC functional connectivity will be *significantly* reduced (i.e., decreased hyperconnectivity) post ADAPT vs. waitlist.

1.2 Secondary Objectives

Brain activations associated with cognitive (PFC), affective (pgACC, AMY), and visceral afferent (INS, thalamus, aMCC, S1 & S2) pain will be significantly more diminished after ADAPT vs. waitlist.

Exploratory Aim. Changes in functional connectivity and brain activations following ADAPT will correspond to reductions in pain (intensity and unpleasantness) and anxiety ratings.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Functional abdominal pain disorders (FAPD) are the most common chronic pain conditions of childhood and are associated with significant functional disability. FAPD impacts >10% of youth in community samples[1,2] and accounts for up to 50% of gastroenterology (GI) visits[3,4]. FAPD is associated with significant functional impairment[5-7], including psychological problems, such as anxiety and depression[8,9]. Youth with FAPD are more prone to social and academic difficulties[7], including school refusal/absences, poor academic performance, and social problems[10]. Impairment and disability are likely to persist, with 25%-45% affected after 5 years [11,12]. Increased healthcare utilization and medical costs are substantial and include invasive and unnecessary medical procedures[13], such as blood work-up (92%), endoscopic studies (51%), and abdominal x-rays (39%). Such work-ups are common, costly ($6,104 per patient), and are associated with medical complications. Although the total cost of pediatric FAPD is unknown, the cost in adults is estimated to be $20 billion a year[14]. Given that a substantial proportion of youth continue to experience symptoms over time and may even develop other chronic pain conditions[15], the total cost of pediatric FAPD is likely substantial. Early and effective intervention may play a key role in preventing long-term problems.

Anxiety is highly prevalent and predicts poor outcomes. A large proportion of youth with FAPD meet criteria for a concurrent anxiety disorder[8,9,16]. Anxiety disorders are characterized by extreme distress and worry and may be generalized or result from specific triggers, such as separation from attachment figures or social situations[17]. In youth with FAPD presenting to GI clinics, anxiety disorders are estimated to affect 42% to 85%[18-20]. Further, prior research[18,21,22] has found that *clinically significant anxiety* is common and predicts increased functional impairment[20,23]. Clearly, youth with FAPD *and* clinical anxiety are the most common and most clinically complicated manifestation of FAPD.

Conventional treatments are ineffective for many youth with FAPD. Pharmacologic treatments (i.e., antispasmodic agents, low-dose psychotropics) for FAPD have limited evidence and efficacy[24]. Cognitive behavioral therapy (CBT) for pain is a conventional non-pharmacologic treatment that uses cognitive strategies (e.g., reducing catastrophic thinking about pain) and behavioral approaches (e.g., activity pacing, behavioral activation) to improve functioning and reduce pain symptoms in youth with chronic pain such as FAPD[25,26]. However, a substantial proportion (~40%) fail to respond[27] and the presence of elevated anxiety can attenuate response to pain-focused CBT[28]. Including specific treatment components to manage clinical anxiety[29,30] is the next logical step for these patients.

Mindfulness may amplify the efficacy of conventional treatments. Mindfulness includes attending to experiences in the present moment and using a nonjudgmental attitude, and is effective for managing pain[31,32] and anxiety[33,34]. Pain reduction following mindfulness in healthy adults has been shown to be related to changes in activation of the primary sensory cortex (S1), insula (INS), anterior cingulate cortex (ACC), and prefrontal cortex (PFC) brain regions[35]. Moreover, improvements in anxiety following mindfulness are characterized by enhanced PFC connectivity with the amygdala (AMY) during resting state[36] and changes in the ACC, PFC, and INS in healthy adults[37].

In general, the neurobiological underpinnings of visceral pain in FAPD are poorly understood although anxiety is likely to play a crucial role in understanding psychological treatment response for pain. Research suggests pain is experienced through the pain connectome[38], a whole-brain-wide network that integrates cognitive, affective, and sensorimotor aspects. Recent reviews of prior neuroimaging studies in IBS, the most common subtype of FAPD, suggest that common areas of activation in response to pain include regions associated with visceral afferent processing, such as the thalamus, INS, anterior midcingulate cortex (aMCC)[39], and the primary and secondary sensory cortices (S1 & S2)[40]. Interestingly, brain regions associated with emotional arousal, including the pregenual anterior cingulate cortex (pgACC) and AMY, are also activated by pain induction in FAPD, but not in healthy controls [39]. In adolescents with FAPD (IBS), structural abnormalities were observed in the INS and S1, in addition to structural and functional abnormalities in the PFC, and posterior cingulate (PCC)[41]. Although brain regions associated with anxiety may play an important role in the expression of pain (i.e., FAPD), there is limited hypothesis-driven research examining the role of anxiety[41]. Anxiety alone is associated with AMY hyperactivations and PFC hypoactivations[42-44].

Neural mechanisms may offer insights on response to a tailored intervention for youth with FAPD. There have only been two research studies examining neural mechanisms of treatment response to non-pharmacologic interventions for FAPD (in adults with IBS). However, these studies use an invasive and potentially risky pain induction technique (rectal distention), though less invasive methods (such as water loading) to induce visceral pain are available[45].The first found that improvements in pain using cognitive therapy were associated with reduced rectal distention-induced activations in the AMY and the pgACC[46]. However, functional connectivity analysis was not undertaken. The second[47] compared hypnotherapy for pain to an educational control and found that the brain response to rectal distension after treatment was

similar to that observed in HCs, suggesting that the treatment had a normalizing effect on the central processing abnormality of visceral pain signals in IBS. Hypnosis responders demonstrated a BOLD attenuation in posterior INS while education responders had a BOLD attenuation in prefrontal cortex. Moreover, in a pediatric pain sample, a positive response to an intensive integrated treatment for complex regional pain syndrome was related to a reduced hyperconnectivity between the lAMY and regions including the PFC[48]; but research specific to pediatric FAPD is needed. Dr. Cunningham's pilot study has shown lAMY-PFC changes in functional connectivity following a symptom provocation task. Further, CBT for pediatric pain (migraine) alters interactions between affective regions (AMY) and structures involved in cognitively driven pain modulation (PFC). Thus, the AMY might represent an important mechanism linking anxiety to sensory processing mechanisms.

These findings suggest that complex neuromechanistic processes account for response to psychological interventions. However, there is no research to our knowledge that distills the mechanism of the effect in a psychological intervention for youth with FAPD and comorbid anxiety. It is plausible that a psychological intervention tailored to anxiety and pain symptoms in FAPD would impact neuromechanisms that link cognitive and visceral afferent processing with emotional arousal (i.e., lAMY-PFC connectivity). Determining such information is critical for identifying brain mechanisms of effective treatments. For example, if lAMY-PFC connectivity is significantly altered following ADAPT (e.g., reduced hyperconnectivy), this evidence would offer further support for the importance of targeting anxiety and pain in youth with FAPD.

2.2 Study Rationale

Given this research evidence, Aim to Decrease Pain and Anxiety Treatment (ADAPT) was developed. ADAPT is a cognitive behavioral approach to manage pain and anxiety for youth with FAPD and comorbid anxiety[49]. For the current study, ADAPT is enhanced with mindfulness meditation. Thus, ADAPT focuses on decreasing attention to pain and anxiety using conventional strategies (CBT), as well as training in mindfulness meditation techniques, such as mindful breathing, developing a mindful awareness of bodily sensations, recognizing the impact of stress on functioning. ADAPT utilizes a blend of 2 interactive sessions with a psychological provider (1 hour, via videoconference) and 4 web-based, self-paced modules (45 minutes) with therapist support videoconferencing and/or phone calls (15 minutes). The Zoom-based ADAPT sessions will be video-recorded. The ADAPT intervention period is approximately 6 weeks (up to eight weeks will be allowed for scheduling flexibility). Based on our prior research[50], there are no known risks associated with the ADAPT intervention.

3. STUDY DESIGN

- **Type/design of trial**: Masked clinical trial
- **Specific statement of the primary and secondary outcomes:** The primary outcome is that left AMY-PFC functional connectivity will be significantly reduced (i.e., decreased

hyperconnectivity) post ADAPT vs. waitlist. The secondary outcome is that brain activations associated with cognitive (PFC), affective (pgACC, AMY), and visceral afferent (INS, thalamus, aMCC, S1 & S2) pain will be significantly more diminished after ADAPT vs. waitlist. We will also explore whether changes in functional connectivity and brain activations following ADAPT correspond to reductions in pain (intensity and unpleasantness) and anxiety ratings.

- **Study population and groups/arms including sample size**: The target population is male and female youth between the ages of 11-16 with functional abdominal pain disorders (FAPD) and clinically significant anxiety. Youth will be recruited from pediatric gastroenterology clinics at Helen DeVos Children's Hospital. We aim to have between 17 – 25 participants in each arm for a total N of 34 - 50 participants in the study. Gender and age will be used as blocking variables in randomization.
- **Study location**: The study is located Helen DeVos Children's Hospital/Spectrum Health.
- **Approximate duration of enrollment period and follow-up:** Participants will be recruited from GI clinics and enrolled in the study during that visit (immediately). They will then come in for the baseline assessment, which will occur approximately one week after enrollment (though up to six weeks after enrollment will be allowed to account for MRI scanner availability). Following that visit, they will then be randomized to either the ADAPT group or a waitlist control group (each six weeks in duration) and will be informed of group assignment within a week of their baseline assessment, and will begin ADAPT/waitlist approximately one week after group assignment (with up to three weeks allowed to begin ADAPT). Up to eight weeks will be permitted for the six ADAPT sessions to account for potential scheduling conflicts and participant illness. Upon completion of ADAPT or waitlist control, participant outcomes will be reassessed at the post assessment visits (approximately six weeks after ADAPT/waitlist). After completing the post assessment visit, participants in the waitlist control group will be given the opportunity to complete ADAPT.

  Participants randomized to ADAPT will be actively involved in the study for a ~10 week period (from screening to post assessment). Those who are randomized to the waitlist control and then opt to receive ADAPT afterwards will be involved for ~16 weeks.

  It is anticipated that we will be actively enrolling participants for 2 years. After study completion, three additional months will be allotted for data analysis.
- **Description of intervention and administration**. In this study, a psychological intervention, Aim to Decrease Anxiety and Pain Treatment (ADAPT), was developed and will integrate mindfulness meditation with cognitive behavioral therapy approaches for managing pain and anxiety to improve patient outcomes. ADAPT is an individual therapy with caregiver involvement that consists of 2 interactive sessions with a psychological provider (60 minutes) once per week for the first two weeks, followed by 4 weeks of self-paced web modules (45 minutes per week) in conjunction with interventionist support (15 minutes per week). Participants will complete the ADAPT program virtually (e.g., using HIPPA compliant videoconferencing or phone). The duration of ADAPT is 6 weeks, although up to eight weeks will be permitted to account for scheduling conflicts and participant illness. Preliminary testing has shown that ADAPT successfully reduces pain and anxiety over time.

  Participants randomized to ADAPT will be actively involved in the study for a ~10 week period (from screening to post assessment). Those who are randomized to the waitlist control and then opt to receive ADAPT afterwards will be involved for ~16 weeks.

- **Randomization, blinding:** Participants will then be randomized to either ADAPT or waitlist control. Gender and age will be used as blocking variables in randomization. For further detail on randomization, see 9.2 *Sample Size and Randomization*. The PI (Cunningham), data analyst (Reeves), and outcome assessors (post-baccalaureate research coordinator) will be blinded to intervention group assignment. The study statistician (Reeves), PI (Cunningham), and mentorship team (Zhu and Arnetz) will be blinded to the primary mechanistic outcome measure. For further detail on blinding, see 6.2.3 *Blinding*.
- **Other protocol specific details**: Participants with FAPD will be recruited from gastroenterology clinics. We will work with Dr. Brittany Barber Garcia (who already provides outpatient clinical/psychological care for patients in the GI clinics) to identify potentially appropriate patients. Of note, the GI section chair, Dr. Cloney is supportive of the project and has agreed to facilitate clinical recruitment and consultation efforts for the study. Dr. Cloney, along with the other GI physicians of the section, are close collaborators of Dr. Brittany Barber Garcia. With Dr. Brittany Barber Garcia's established relationships within GI, we will be able to work broadly with members of the GI team at HDVCH.

  Potentially appropriate participants will be contacted by a member of the medical team and/or by a study staff member. They will be described the study in detail and participants will have the opportunity to ask questions and voice concerns. If the patient/family is agreeable, informed consent/assent will be obtained and participants will be screened for study eligibility. Qualifying patients will then be scheduled to complete the baseline assessment visit (clinical measures/WL-SPT with fMRI). After this visit, participants will be randomized to either the ADAPT treatment group or a waitlist control (each condition will last for approximately 6 weeks). The post assessment will be similar in format to the baseline assessment. Those randomized to waitlist will be eligible to receive ADAPT after the post assessment.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

The study population is male and female youth between the ages of 11-16 diagnosed with functional abdominal pain disorders (FAPD) and clinically significant anxiety. We plan to approach approximately 124 participants, ages 11-16 years. Of those, we expect 75% will agree to participate (n=93) based on our pilot fMRI study. Of those, we expect approximately 65% will qualify. Thus, we anticipate recruiting n=60 to complete a baseline assessment. Based on our previously RCT, we expect 85% of those recruited in clinic will complete the baseline assessment (n = 50) and the majority will be retained in the study (90%, n=45). Based on our fMRI pilot study, we expect to lose approximately 10% of participant data to movement artifacts yielding n=40 with usable data. The minimum number of total completed participants allowed will be 34 and the maximum will be 50.

We will recruit males and females to participate in this study. While FAPD is more common in females, we have found that we are easily able to recruit males as well. Based on our prior research projects, we expect that we will recruit a sample of youth with FAPD that is 65% female and 35% male. The PI (Cunningham) will check in with the mentorship team (Arnetz and Zhu) quarterly regarding enrollment and gender breakdown in a blinded fashion. If the gender breakdown is skewed (>85% females or >60% males), the PI (Cunningham) will problem solve with study mentors (Arnetz and Zhu) to ensure the sample is representative of the

population. Recruitment efforts would target candidates from underrepresented gender until the sample is more representative of the FAPD population.

4.1 Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study.

- Children (males and females) between 11 and 16 years of age and their parent/primary caregiver will participate in the study.

Child Criteria

- Meets criteria for FAPD based on physician diagnosis of FAPD and ROME IV FAPD criteria (see *Description of Evaluations* section for additional details).
- Meets criteria for presence of clinically significant anxiety (based on the Screen for Child Anxiety Related Disorders [SCARED] total cut-off score ≥ 25; see *Description of Evaluations* section for additional details).

Child and Caregiver Criteria

- Youth and caregiver must have sufficient English language ability necessary to complete study measures and protocol.

4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at screening will be excluded from study participation.

Child Criteria

- Children with a significant medical condition(s) with an identifiable organic cause including those that may include abdominal pain symptoms (e.g., Inflammatory Bowel Diseases).
- Children with a documented developmental delay(s), autism spectrum disorder, a previously diagnosed thought disorder (i.e., psychosis), or bipolar disorder.
- Significant visual, hearing, or speech impairment.
- Organic brain injury.
- Participants who are currently in psychological therapy for pain or anxiety.
- Participants with severe depressive symptoms (T score ≥ 80) or current active suicidal ideation reported on the CDI.
- Exclusionary criteria specific to the fMRI component of the study:
- Participants with an implant such as a cochlear implant device, a pacemaker or neurostimulator containing electrical circuitry or generating magnetic signals. Participants with any significant ferrous material in their body that could pose the potential for harm in the fMRI environment or cause signal suppression of key regions (i.e. orthodontia).
- Female participants who report current/suspected pregnancy.
- Participants with evidence of claustrophobia.

Child and Caregiver Criteria

- Inability or unwillingness of individual or legal guardian/representative to give written informed consent.

4.3 Study Enrollment Procedures

- **Method for identifying and recruiting candidates for the trial**. Eligible participants with FAPD will be identified for the study from new or existing patients seen at the outpatient pediatric GI clinics.
- **Procedures for documentation of reasons for ineligibility and for non-participation of eligible candidates.** A screening log will be maintained with eligible candidates contacted/approached for study recruitment. This log will detail reasons for ineligibility and/or reasons for disinterest in study participation if applicable. Once consented, participant names and ID numbers will be recorded in a secured enrollment log. A separate log will track participant progress throughout the study.
- **Consent procedures.** FAPD patients will be introduced to the study in person (or virtually if an in-person option is not available) by a medical staff member and/or study staff member who will explain the study to the patient and the primary caregiver in greater detail. Participants will be assured that their usual medical care will not be affected based upon whether or not they choose to participate. Written consent from the primary caregiver and written assent from the child will be obtained by study staff. All participants will be notified that screening is necessary and study entry is not guaranteed at this point. If the child is not eligible and the family is interested in the child receiving mental health services, contact information for the psychology service at HDVCH will be provided.
- **Randomization procedure for assigning a participant to an intervention group.** Following the baseline visit, patients will then be randomized to either the ADAPT group or a waitlist control group (each six weeks in duration) and will be informed of group assignment within a week of their baseline assessment, and will begin ADAPT/waitlist approximately one week after group assignment (with up to three weeks allowed to begin ADAPT). Gender and age will be used as blocking variables in randomization.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Participants will either begin ADAPT in the week following the treatment group assignment or after completing the post assessment (waitlist control). The duration of ADAPT is 6 weeks (although up to 8 weeks will be allowed for scheduling flexibility) and a total of 6 hours of intervention will be administered. Participants will be reminded via text message to complete their respective ADAPT web modules. Based on our prior research, the risk for potential for adverse events is low.

5.2 Handling of Study Interventions

ADAPT will be primarily delivered by a trained interventionist (Dr. Barber Garcia, licensed clinical psychologist). Dr. Barber Garcia is a trained provider with expertise in pediatric pain management and telehealth. In addition, a back-up provider will be available to deliver the intervention in the event of an absence of the primary provider.

5.3 Concomitant Interventions

Any concomitant interventions (i.e., medical and psychological) experienced by the participants (either allowed or prohibited) will also be assessed for and recorded at baseline and post assessments. Participants will provide the reason and duration of concomitant interventions at the baseline and post assessment visits.

5.2.1 Allowed Interventions

Participants are allowed to continue their medical care as usual (i.e., taking medication) throughout the duration of the study. Participants are also allowed to partake in psychological therapy as long as it is not directly addressing pain or anxiety.

5.2.2 Required Interventions

There are no other required interventions.

5.2.3 Prohibited Interventions

Youth who are currently in psychological therapy for pain or anxiety will be excluded from participation.

5.4 Adherence Assessment

The projected sample size is not adequately powered to account for differences in adherence. However, data will be collected on the attendance of Zoom-based sessions, completion of web-based content, and completion of therapist videoconferencing/phone calls, in addition to completing study assessments. We anticipate good adherence (>80% completion of intervention materials) based on our prior research. If adherence becomes problematic during the course of the study, the interventionist (Barber Garcia) will communicate these concerns with the PI (Cunningham).

6. STUDY PROCEDURES

(See subsections below)

6.1 Schedule of Evaluations

Assessment	Screening	Baseline Assessment		ADAPT Session 2	ADAPT Session 6	Post Assessment		Post WL/ ADAPT*
	Participant	*Participant*	*Parent*	*Participant*	*Participant*	*Participant*	*Parent*	*Participant*
fMRI/Water loading measures								
Current pain intensity/unpleasantness		X				X		
State Anxiety (VAS)		X				X		
Fullness Rating Scale (during fMRI)		X				X		
Self-Report/Interview measures								
Screen for Anxiety and Related Disorders (SCARED)	X		X			X	X	X
Eligibility Criteria	X							
FAPD screening measure	X					X		
MRI Safety and Screening	X							
CDI	X					X		
Menstruation Query	X	X				X		
Other Pain		X				X		
Petersen Pubertal Development Scale (PDS) (*also includes menstruation query)		X				X		
PROMIS Pain Interference		X				X		
Edinburgh Handedness Inventory		X				X		
Pain VAS Scale	X	X	X			X	X	
Pain NRS Scale	X							X
Functional Disability Inventory (FDI)	X	X	X			X	X	X
Pain Catastrophizing Scale		X	X			X	X	
Affective Reactivity Index (ARI)		X	X			X	X	
Self-Efficacy Chronic Pain Scale		X	X			X	X	
Depression Anxiety Stress Scales (DASS)			X				X	
Demographic Information			X				X	
Child Pain History & Sociodemographic Factors			X				X	
Concomitant Medications			X				X	
Adverse Event Query Form				X		X		X
Child COVID-19 Related Distress		X				X		
Child COVID-19 Related Distress Coping					X			X
COVID-19 Exposure and Family Impact Survey (CEFIS)			X				X	
Adverse Childhood Experiences (ACEs)			X				X	

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

Consenting will be completed with a single informed consent form that describes both the screening and study procedures. Patients with FAPD and their primary caregiver will be introduced to the study by a medical staff member and/or study staff member at their outpatient pediatric GI medical visit, or virtually if an in-person option is not available. If the patient expresses interest in the study after being introduced to the study by their GI medical provider and research staff are unable to meet with them in-person for their clinic appointment, a screening appointment will be made outside of the office visit. FAPD diagnosis will be confirmed with the patient's provider using the EMR and/or direct communication. A member of the research staff will explain the study to the patient and primary caregiver in greater detail. Participants will be assured that their usual medical care will not be affected based upon whether or not they choose to participate. Participants and caregivers will be informed about the importance of confidentiality and will agree that they will not share any personal or health information about other study participants. If interested, the patient and their caregiver will complete the consent, and assent. All consent and assent forms will be stored in a secure location within the Secchia Center.

Screening

Patients are consented and screened within the same study visit. Immediately upon providing assent/consent, participants will complete the Screen for Child Anxiety and Related Disorders (SCARED), the Functional Disability Inventory (FDI), the Numeric Rating Scale (NRS) for pain intensity, and the Children's Depression Inventory (CDI) before leaving their GI clinic appointment. If the patient does not qualify based on their scores from the anxiety measure, they will not be administered the remaining screening measures. For potentially eligible participants, the participants and families will answer questions to ensure the child can safely enter the scanner and undergo fMRI and study procedures. Additionally, study staff will complete the ROME IV FAPD diagnostic checklist with the participant's gastroenterology provider to ensure that the child meets FAPD criteria. These procedures will ensure that eligibility is determined prior to assessment or randomization. Participants who can complete the fMRI protocol procedures, evidence clinical anxiety, do not evidence severe depressive symptoms (T score $\geq$ 80) and meet FAPD criteria will be considered eligible for participation. If eligible, we will inquire whether females have achieved menarche. If yes, we will query the date of their last menstrual cycle and inform them that we will schedule the neuroimaging on a date when they are not having pain due to menstruation. If the patient expresses interest in the study after being introduced to the study in-person by their GI medical provider and research staff are unable to meet with them in-person for their clinic appointment, a screening appointment will be made outside of the office visit. FAPD will confirmed with the patient's provider using the EMR and/or direct communication.

Screening Measures:

- *Screen for Child Anxiety Related Disorders, SCARED* [51]. Child reported anxiety in the past 3 months; ≥25 is clinical anxiety. This measure has been recommended for use by the American Academy of Pediatrics [52] and has been validated in pediatric chronic pain [51,53,54] and used in pediatric FAPD samples[20,28].
- *Rome IV FAPD Diagnosis Checklist (physician report).* FAPD criteria based on the Rome IV. FAPD include irritable bowel syndrome (IBS), functional dyspepsia, abdominal migraine, and FAPD- not otherwise specified. To meet criteria for FAPD, a child must endorse continuous or episodic pain at least 4 times in a month that do not exclusively occur during a physiological event (e.g., eating, menses) for a periods of 2 months or longer that cannot be fully explained by another medical condition after appropriate evaluation. This questionnaire will allow us to group our sample into specific diagnostic subtypes of FAPD.
- *MRI Safety and Screening.* Research staff to determine if patient can safely complete fMRI protocol.
- *Children's Depression Inventory 2 (CDI)*[55]. A validated and reliable measure of depressive symptoms in the past 2 weeks.
- *Menstruation Query.* Female participants will be asked if they have achieved menarche. If participants indicate that they have, we will query the date of their last menstrual cycle and inform them that we will schedule the neuroimaging on a date when they are not having pain due to menstruation. This may include pain that a child reports occurs in the days prior to menstruation if applicable.
- *Functional Disability Inventory (FDI)*[56]. 15-item measure of physical/daily function in last few days. This measure has been validated in pediatric chronic pain [57] and used in pediatric FAPD samples[20,28].
- *Numeric Rating Scale (NRS)*[71] for pain. Average, highest, and lowest pain levels in the past week will also be assessed.

6.2.2 Enrollment, Baseline, and Randomization

Enrollment

A research team member will attend GI clinics at Helen DeVos Children's Hospital when possible. They will consult with a physician about whether attending patients may meet criteria for the study. If patients potentially meet criteria and are interested, our research team will approach/contact patients after the physician has introduced the study. For those families who may be interested/potentially eligible but are not available at the time of their medical visit, a follow up visit will be scheduled with the patient/family to determine eligibility.

Enrollment is defined as the date all of the screening criteria are met and the

individual agrees to participate. This date will be recorded on a CRF.

Baseline Assessments

Qualifying participants and their respective caregivers will be scheduled to complete an in-person baseline assessment. Participants will complete additional study measures. Caregivers will complete several measures pertaining to their child's pain and child's worries in addition to a measure of their own psychological symptoms. Participants and caregivers will be given the option to either complete these measures during their baseline assessment visit or before this visit using their own electronic device (to reduce the length of the in-person visit). Participants will enter the MRI scanner, where scans of brain structures and cerebral blood flow will be performed while participants provide current pain ratings. Participants will then exit the scanner to undergo the WL-SPT, a validated non-invasive procedure for youth ages 8-16 to create visceral pain sensations (40). This task has also been used in adults with FAPD[70].

Participants will ingest water until they have achieved complete fullness eliciting discomfort (~5 minutes). Then, participants will re-enter the scanner and resume functional imaging.

- Imaging: *Pre-WL-SPT*. During imaging, the first 10 minutes will consist of positioning the participant and collecting structural images. BOLD and PCASL acquisitions will be obtained. *Post-WL-SPT*. Following the WL-SPT, BOLD AND PCASL acquisitions will also be obtained.

Participants will then be randomized within one week of their baseline assessment. Approximately one week after randomization, participants will complete either 6 weekly sessions of ADAPT or 6 weeks of waitlist.

Families will receive payment for this study in the form of an Amazon gift card. We will reimburse participants $100 for each assessment visit (baseline and post assessment for up to $200 total).

Baseline participant measures:

- *Functional Disability Inventory (FDI)*[56]. 15-item measure of physical/daily function in last few days. This measure has been validated in pediatric chronic pain [57] and used in pediatric FAPD samples[20,28].
- *Visual Analog Scale (VAS)*[58] for pain. Average, highest, and lowest pain levels in the past week will also be assessed.
- *Numeric Rating Scale (NRS)*. Administered only during instances where the electronic or physical VAS slider cannot be used (e.g. technical difficulties).
- *Self-Efficacy Pain Scale- Child Version*[59]. A valid and reliable measure of child self-efficacy when in pain.
- *Affective Reactivity Index (ARI)- Self- Report*[60]. A valid 7-item measure of irritability in the last 7 days.
- *Pain Catastrophizing Scale for Children*[61]. A valid measure of maladaptive beliefs about pain and feelings experienced when in pain.
- *NIH PROMIS Pain Interference*[62]. A valid measure of functional impairment due to pediatric pain in the past 7 days.
- *Peterson Pubertal Developmental Scale (PDS)*[63]. A valid and reliable pubertal status assessed via clinician interview.

- *Menstruation Query.* Female participants will be asked if they have achieved menarche. If participants indicate that they have, we will query the date of their last menstrual cycle, and inform them they we will schedule the neuroimaging on a date when they are not having pain due to menstruation. This may include pain that a child reports occurs in the days prior to menstruation if applicable.
- *Other Pain.* Participants will be queried about other pain sources besides abdominal pain.
- *Edinburgh Handedness Inventory*[64]. A validated measure that assesses the dominance of a person's right or left hand in everyday activities. For the purposes of this study, one original item was removed (striking a match) given our pediatric sample.
- *Child COVID-19 Related Distress.* An item assessing the child's distress in relation to the COVID-19 pandemic.

Baseline caregiver measures:

- *Child Pain History & Sociodemographic Factors*. Demographic factors, school absences, pain duration, location, and concomitant psychological treatments
- *Depression Anxiety Stress Scales*[65]. A validated and reliable measure of parent depression, anxiety, and tension/stress.
- *Visual Analog Scale (VAS)*[58]. Parent reported average pain experienced by their child over the past 2 weeks.
- *Numeric Rating Scale (NRS).* Administered only during instances where the electronic or physical VAS slider cannot be used (e.g. technical difficulties).
- *Parent Pain Catastrophizing Scale (PCS)*[66]. Validated measure of maladaptive beliefs about child pain.
- *Screen for Child Anxiety Related Disorders- Parent Report, SCARED*[51]. Parent-reported child anxiety symptoms over the past three months; ≥25 is clinical anxiety. This measure has been used in pediatric FAPD samples[20,28].
- *Functional Disability Inventory (FDI)- Parent Report*[56]. 15-item measure of child physical/daily functioning in the past few days. This measure has been used in pediatric FAPD samples[20,28].
- *Self-Efficacy Chronic Pain Scale- Parent Version*[59]. Parent reported child self-efficacy during pain. This measure has been validated.
- *Affective Reactivity Index (ARI)- Parent- Report*[60]. A valid and reliable 7-item measure of child irritability.
- *Concomitant Medication Form.* Concomitant medication information (medication name, reason for taking, unit, frequency, route, etc.) and therapies will be obtained via chart review prior to the baseline visit. Study staff will confirm with caregivers that the information is correct and up to date at the baseline and post assessment visits. Any changes in medication from baseline to post assessment will be documented.
- *COVID-19 Exposure and Family Impact Survey (CEFIS)*[67]. A measure from the Center for Pediatric Traumatic Stress to capture the impact of the COVID-19 pandemic on families and caregivers.

- *Adverse Childhood Experiences (ACEs)*[68]. A valid, 9-item measure used by the National Survey of Children's Health that assesses for adverse events occurring in childhood before the age of 18.

Measures administered during fMRI:

- *Pain Intensity and Unpleasantness Visual Analog Scales (VAS)*[58,69]. Pain intensity is associated with nociceptive processing and is a common measure of treatment response[26]. Pain unpleasantness is related to affective network activity[35], and is highly responsive to meditation[35].
- *State Anxiety (VAS)*[70]. 0-10 self-report of how anxious the child is feeling in the present moment.
- *Fullness Rating Scale*[45]. Youth will be asked to indicate how full they felt after water ingestion by selecting from images representing different levels of fullness, from empty (coded 0) to full (coded 4).

Randomization

Following the baseline visit, patients will then be randomized to either the ADAPT group or a waitlist control group (each approximately six weeks in duration) and will be informed of group assignment within a week of their baseline assessment, and will begin ADAPT/waitlist approximately one week after group assignment (with up to three weeks allowed to begin ADAPT). For additional details, see 9.2 Sample Size and Randomization.

6.2.3 Blinding

- **Procedure for retaining the blind.** Blinding of study personnel will be employed when possible (Table 1). Of note, our study statistician (Dr. Mathew Reeves) will only have access to subject IDs and Treatment A and Treatment B. He will generate monitoring reports for closed sessions based only on Treatment A and Treatment B. If there is an issue of serious concern (e.g., safety issues in one arm, differential attrition etc.) that requires complete unblinding, Dr Reeves will identify another statistician to run the unblinded reports. Dr. Reeves will also complete final analysis only by Treatment A versus B and the code will be revealed only after the data has been analyzed. Furthermore, the PI (Cunningham) will be blinded to group assignment. However, Dr. Barber Garcia will not be blinded to group assignment as study interventionist and to ensure the safety of participants and the integrity of the study. It is critical for Dr. Barber Garcia (a licensed clinical psychologist) to be aware of participants who are randomized to the ADAPT intervention to perform her role (and in the case of a back-up provider) to ensure patient safety (e.g., risk assessment for suicidal ideation, trauma/abuse, etc.) during the study. The PI (Cunningham) and study mentors (Zhu, Arnetz) will have no access to post-assessment data by group assignment until after the completion of the study.
- **Individual authorized to break the blind.** Dr. Barber Garcia will be authorized to break the blind. She will not be blinded to group assignment

and therefore can determine if the study team's blind should be broken in cases where a patient's safety is in question. Dr. Barber Garcia's extensive experience as a pediatric psychologist make her appropriately equipped to manage this responsibility.

- **Circumstances for breaking the blind.** The blind will be broken at the clinical discretion of Dr. Barber Garcia. Circumstances for breaking the blind may include cases when a patient's safety is at risk, differential attrition, or if a patient's symptoms remarkably worsen throughout treatment.
- **Procedure for breaking the blind**. If the blind needed to be broken, Dr. Barber Garcia would communicate with our local IRB, any NCCIH members involved in the study, and involve our study team, included but not limited to the PI (Cunningham), co-mentors (Zhu, Arnetz), the biostatistician (Reeves), and the outcome accessors (post-baccalaureate research coordinator).

Table 1. Blinding of Study Personnel.

Stake holder	Intervention group assignment	Primary Mechanistic Outcome Measure	Clinical/ Functional Outcome Measure
Study subjects	Subjects will be aware if they are randomized to ADAPT versus waitlist.	The subjects will participate in the collection of this data but will not be involved in the interpretation of the data or the analysis of the results.	Subjects will provide such data. As such, they will be aware of their own responses on clinical/functional outcome measures.
Interventionists licensed clinical psychologist (Barber Garcia), backup interventionist	The interventionist will know if participants are randomized to the intervention group.	The interventionist will not be involved in analyses.	The interventionist will not be involved in analyses.
Outcome Assessors (post-baccalaureate research coordinator)	Outcome assessors will be blinded as to group assignment.	The outcome assessor will be involved in the collection of such data, but will not be involved in the interpretation and analysis of results.	The study coordinator will serve as an outcome assessor. However, data will be collected directly from participants using online forms. In addition, the study coordinator will only access/manage post-assessment data that has been de-identified (with group assignment removed).
Data Analysts/Statistician (Reeves)	The study statistician will be blinded to the group assignment.	The study statistician will be blinded until the completion of this study	The study statistician will generate reports and submit data as requested by NCCIH or the IMC

			for the duration of the study.
Principal Investigator (Cunningham) and Study Mentors (Zhu, Arnetz)	The PI will be blinded to intervention group assignment.	The PI and her mentorship team will be blinded to post-assessment data results until after the completion of the analysis. She will participant in processing/management of fMRI data without knowledge of group assignment.	The PI and her mentorship team will be blinded to post-assessment results by group assignment until after completion of the analyses.

6.2.4 Adverse Event Queries/Additional Measures

ADAPT Session 2:
Participants will be queried about any experienced adverse events during their second session of ADAPT (if randomized to ADAPT treatment group). This form will also be administered at post assessment. For those randomized to waitlist, they will complete this form at post assessment, ADAPT sessions 2 and 6 (if they opt to complete ADAPT).

- *Adverse Event Query Form*. A form to be completed via clinician interview assessing for adverse events experienced by participants.

ADAPT Session 6
During the last session of ADAPT, participants (in both the ADAPT treatment and waitlist control groups) will be queried as to whether they found the ADAPT intervention helpful when coping with distress related to COVID-19.

- *Child COVID-19 Related Distress Coping.* An item assessing whether the intervention was helpful in improving the child's coping with distress in relation to the COVID-19 pandemic.

ADAPT measures for those completing the intervention after waitlist (i.e., after post assessment)
Those randomized to the waitlist condition will be eligible to receive ADAPT after their post assessment. Waitlist control participants who choose to complete the ADAPT program after their post assessments will complete brief measures (e.g., anxiety, disability, pain) and will be queried about adverse events during the second session of ADAPT and via phone or videoconferencing following their last ADAPT session.

- *Screen for Child Anxiety Related Disorders, SCARED*[51]
- *Functional Disability Inventory (FDI)*[56]
- *Visual Analog Scale (VAS)*[58] for pain

- *Child COVID-19 Related Distress Coping*
- *Numeric Rating Scale (NRS)*[71] for pain (if VAS not obtained)
- *Adverse Event Query Form*.

6.2.5 Completion/Final Evaluation

A post assessment (including fMRI) will be completed for all participants approximately one week after completion of treatment or waitlist. Participants will complete the same assessment measures and procedures as administered at the baseline assessment in addition to measures that were administered at screening. Upon completion of this visit, participants will receive a $100 gift card (Amazon; described in further detail in *6.2.2. Enrollment, Baseline, and Randomization*).

Post assessment participant measures:

- *Screen for Child Anxiety Related Disorders, SCARED*[51]
- *Functional Disability Inventory (FDI)*[56]
- *Visual Analog Scale (VAS)*[58] for pain
- *Numeric Rating Scale (NRS)*[71] for pain (if VAS not obtained)
- *Rome IV FAPD Diagnosis Checklist*
- *Children's Depression Inventory 2 (CDI)*[55]
- *Self-Efficacy Pain Scale- Child Version*[59]
- *Affective Reactivity Index (ARI)- Self- Report* [60]
- *Pain Catastrophizing Scale for Children*[61]
- *NIH PROMIS Pain Interference* [62]
- *Peterson Pubertal Developmental Scale (PDS)*[63]
- *Menstruation Query*
- *Other Pain*
- *Edinburgh Handedness Inventory* [64]
- *Adverse Event Query Form*
- *Child COVID-19 Related Distress*

Post Assessment caregiver measures:

- *Child Pain History & Sociodemographic Factors*.
- *Depression Anxiety Stress Scales*[65].
- *Visual Analog Scale (VAS)* [58].
- *Numeric Rating Scale (NRS)*[71] for pain (if VAS not obtained)
- *Parent Pain Catastrophizing Scale (PCS)*[66].
- *Screen for Child Anxiety Related Disorders- Parent Report, SCARED*[51].
- *Functional Disability Inventory (FDI)- Parent Report*[56]
- *Self-Efficacy Chronic Pain Scale- Parent Version* [59]
- *Affective Reactivity Index (ARI)- Parent- Report* [60]
- *Concomitant Medication Form*
- *COVID-19 Exposure and Family Impact Survey (CEFIS)*

- *Adverse Childhood Experiences (ACEs)*

Measures administered during fMRI:

- *Pain Intensity and Unpleasantness Visual Analog Scales (VAS)* [58,69] *State Anxiety (VAS)*[70]
- *Fullness Rating Scale*[45]

7. SAFETY ASSESSMENTS

Participant safety will be monitored once an individual is enrolled in the study. Potential risks and adverse events are listed below:

- **Emotional Distress.** Given the risk of elevated anxiety and mood problems in individuals with FAPD, some responses on these measures may reveal anxiety, depressive affect, and/or suicidal thoughts. Youth may also find some questions embarrassing or uncomfortable to talk about. To help reduce potential discomfort, the research protocol includes standardized measures. Suicidal ideation may be directly queried during the depressive symptom screener. Participants' responses will be monitored to assess any safety issues such as suicidal ideation. Although ADAPT online modules do not specifically elicit responses that may reveal depression/suicidal ideation, such symptoms (anxiety and mood) may arise during ADAPT. A safety assessment will occur via telephone if indicated. ADAPT is an evidence-based intervention and has not been found to be associated with any adverse effects. All participants will continue to receive their medical care as usual during the study.

  In the event that a participant reveals severe depressive symptoms or suicidal ideation, the following steps will be taken: (1) Dr. Barber Garcia, the co-investigator (licensed clinical psychologist) will address these concerns, (2) a professional and confidential risk assessment, including detailed information about suicidal ideation, intent and/or plans, access to means to hurt themselves, major stresses, availability of social supports, access to treatment, and plans for safety will be discussed in detail with the participant and their parent. The assessment will be conducted by the interventionist (Barber Garcia) and (3) a referral to the ER and/or a referral to the Psychiatry Division or an outpatient Psychology clinic, as appropriate, will be made. If the family refuses to follow through on the aforementioned recommendations, we will contact the appropriate authorities as warranted to ensure the safety of our participants. All actions will be documented.

  Of note, all participants will be carefully screened for depressive symptoms and suicidal ideation using a validated measure *prior to* engaging in the fMRI portion of the study. Those who have high levels of depression and/or active suicidal ideation (T score ≥ 80) will be referred for mental health care and will not be eligible for the study.

  During assessment and/or treatment procedures, participants may reveal experiences of abuse to the assessor or study therapist. In the event that the project staff becomes aware of suspected or actual abuse or neglect, Dr. Barber Garcia will be notified. A report will be immediately filed with the appropriate state agency when necessary. The informed consent/assent procedures specify that confidentiality will be

breached if research staff learn that a minor is the victim or suspected victim of abuse or neglect.

- **fMRI related Risks**. fMRI has been approved for routine research and clinical applications and does not pose any known risk to participants. There are no known risks from exposure to the magnetic fields and radio waves used during fMRI data collection. However, it is not assured that harmful effects will not be recognized in the future. A known risk is that strong magnetic fields attract iron or steel metal objects, thus posing a safety risk. Prior to participation in the fMRI scans, participants will be given questionnaires to determine if they if they are eligible to complete the fMRI procedure. If they have metal objects in their bodies, they will be excluded from participating in the study. In addition, any removable metal (e.g., glasses, watch, clothes with zippers) on the day of imaging will be removed before the participant enters the fMRI rooms.

  In addition, it is possible that participants may feel uncomfortable or confined once inside the imaging machine. Any participant who experiences discomfort or exhibits distress will be monitored visually and via microphone to ensure they are tolerating the procedure. In addition, an alarm system is used to monitor the temperature and air. As the scanner is very loud, participants' hearing will be protected with noise-reducing headphones specifically designed for use in the fMRI scanner. Finally, as participants are lying in a supine position, the child may at times feel sleepy or bored. If participants express a desire to leave the machine, either temporarily or permanently at any point, they will be removed immediately.

- **Time Commitment and Fatigue.** The assessment visits will require approximately a two hour time commitment (clinical measures/fMRI visit), which may cause slight discomfort. Assessors will be trained to assess fatigue and will give participants a 5-10 minute break if needed. For ADAPT sessions, there should be minimal discomfort due to the shorter length of these sessions (60 minutes or less).

  Participants will be informed of their right to refuse to participate in any part of the data collection and will be given the phone numbers of the Principal Investigator as well as the Institutional Review Board of MSU in the event that they desire further information or would like to issue a formal complaint.

- **The water loading task** is a non-invasive and validated procedure for induction of abdominal discomfort in youth with FAPD. The procedure was validated by Walker and colleagues (2006). Children are, by design, likely to experience abdominal discomfort during the task. The procedure produces symptoms similar to, but less intense, than those naturally experienced by children with FAPD. As noted by the authors, "This level of discomfort was acceptable to children and their parents" (Walker et al., 2006, p. 710). It will be explained to families that participation is completely voluntary and that they may drop out of the study at any time, for any reason, and that this will not affect the child's medical care.

  There is a small risk of vomiting if children consume water beyond the point of feeling completely full. During the water load period, children will be asked to rate their fullness at 5-minute intervals – to make sure they do not push themselves to consume water beyond the point of perceived fullness. One child (out of 230) in Walker's original

study vomited following water ingestion. “During debriefing, the child reported that he had pushed himself to drink water beyond the point of feeling full. In subsequent administrations of the water load, children were cautioned that vomiting was a possibility if they continued to consume water beyond the point of feeling completely full,” (Walker et al., 2006; p. 707). We will caution children similarly in our study.

Another unlikely concern is exceptionally rare occurrence of water toxicity. To eliminate this risk, a daily fluid maintenance formal will be used based on their weight to determine the maximum fluid value for each child. The amount of water will be capped at that value (up to 1.5 L). Further, allowing a specific time frame (up to 15 minutes) creates conditions to make water toxicity impossible.

Study staff will be on hand to ensure the participant stops drinking water after a complete sensation of fullness. We will contact the on-call GI physician at HDVCH in the event of any questions/concerns that may need immediate attention. In addition, participants will be instructed that they are free to terminate the task at any time.

Risk/Benefit Analysis: The risk/benefit ratio is favorable for this study and adverse events are not anticipated. Overall, the study does not significantly increase the participants’ risk of harm beyond those risks that are inherent in ordinary daily living. All study procedures can be terminated immediately. In addition, all participants will be able to receive an evidence-based intervention (ADAPT). Preliminary data suggests this intervention has a positive impact on symptoms associated with FAPD and comorbid anxiety. Information obtained from this study will be valuable for refining behavioral interventions for the treatment of youth with chronic pain and comorbid anxiety.

7.1 Specification of Safety Parameters

We expect no adverse events based on prior research we’ve conducted. However, precautions will be taken to ensure patient safety as detailed above.

The imaging protocol used in this study includes only the minimum MR scanning needed to execute the tasks and paradigms for the research project. No report will be generated or supplied to the research participants. However, all scans performed for this project will be reviewed for gross abnormalities by a radiologist to be named prior to any subject enrollment. All research studies at SH have a radiologist assigned to read images. We will work with Dr. Mark DeLano, Director for the Division of Radiology and Biomedical Engineering at MSU, and Medical Director of Adult Radiology at SH to assure similar processes are executed for our study. Moreover, our neuroimaging mentor Dr. David Zhu will provide oversight and has established relationships with the SH radiology team and will help ensure the safety of our participants and the clinical procedures. . Although no diagnosis will be made, in the event that abnormal findings are identified, the investigator (Cunningham) will be informed and will assume responsibility for notifying the participants.

In the case that abnormal findings are identified, the participant’s physician (identified via the patient’s electronic medical record) will be contacted by the PI (Cunningham), or a designee of the PI (such as the research coordinator), and the findings will be reported. A report generated by the identified radiologist will be made available to the physician if requested.

For clinically significant findings of neuroimaging, the participant may choose to obtain appropriate clinical care or seek a second opinion. This might change the participant's insurability and employability as it relates to the clinical finding only. Seeking care may place the participant at risk for unforeseen medical costs, particularly for conditions that are benign. However, the presumption is that detection of a potentially clinically significant finding will prove to be beneficial. In the event of incidental findings, the neuroimaging mentor (Zhu) will be consulted to determine if the abnormal finding precludes participation.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

We anticipate that ADAPT will be associated with low risk based on our prior research[50]. In addition, we will carefully monitor for adverse events, including a specific form administered to participants (post-assessment, ADAPT session 2, and, for those completing ADAPT after the waitlist period, session 6.)

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

Adverse events and unanticipated problems will be carefully monitored and documented at each study visit. During all phases of the study (i.e., assessment and treatment), adverse events and unanticipated problems (whether or not they are thought to be study-related) will be monitored and documented in several ways.

1) During screening, assessments, and for those completing the ADAPT intervention, the interventionist (Barber Garcia) will maintain an individual log to record any increases in pain or mood-related problems during the study. Dr. Barber Garcia will review these logs each week.

2) In addition, the study team will have quarterly meetings to monitor the progress of the study, the integrity of the treatment, discuss the need for any protocol refinements, and conduct regular safety monitoring checks of adverse events and unanticipated problems. Severe depressive symptoms or active suicidal ideation will be recorded as an adverse event.

3) Any adverse events/unanticipated problems reported during the study including during the assessment (e.g., measures and fMRI/water loading) or during ADAPT sessions will be immediately brought to the attention of the study team. The IRB requires yearly renewal of study protocols, which provides additional monitoring of participant safety. The study team will review study data to ensure safety compliance and proper reporting to the IRB.

7.4 Reporting Procedures

Case report forms for AEs and SAEs have been developed. An AE documentation form will be completed by a clinician at the second ADAPT session and during the post assessment. For those randomized to waitlist control who are completing ADAPT after the post assessment, they will complete this information during session 2 and 6 of ADAPT in addition to the post-assessment query. The form documents whether or not an adverse event has occurred and throughout the trial if any AEs/SAEs are spontaneously reported by participants. AEs will be reported by body system and rated by level of severity (mild, moderate, severe, life-threatening). The primary study team will meet regularly to monitor the progress of the study and safety of participants in blinded fashion. Reportable events will also be recorded in a separate study database.

For any adverse event meeting the definition of "severe" or "life threatening," the study interventionist (Barber Garcia) and research coordinator will communicate with one another to complete a "Serious Adverse Event" reporting form within one working day. Any severe or life threatening adverse event report will be sent to the IMC and the IRB will be notified.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the investigator becoming aware of the problem.

7.5 Follow-up for Adverse Events

A study team member will provide referrals, as appropriate, for treatment needs resulting from any adverse events or unanticipated problems. In the event of any medical concerns that arise, the research staff will contact the on-call GI physician at HDVCH.

7.6 Safety Monitoring

The team will also report any significant study-related or unanticipated adverse events to the Institutional Review Board and to the study sponsor based upon institutional and sponsor guidelines. In addition, there are three Independent Monitoring Committee (IMC) members with expertise in radiology, psychiatry, and biostatistics who will assess the safety and study-related concerns. Two IMC members have expertise in pediatric research. Specifically, the member with expertise in biostatistics has a program of research pertaining to the assessment and psychological treatment of depression in Hispanic adolescents (Dr. Brincks). The member with expertise in psychiatry (Dr. Familiar) has a program of research on the identification of risk factors and outcomes in children and adolescents with chronic health conditions including HIV. Given that this study investigates the intersect of

pediatric chronic health conditions and mental health functioning, this experience and expertise is highly complementary. In addition, our radiologist member is well suited to assess MRI related issues/concerns. Any reportable events that occur (which includes the occurrence of any safety issues related to the scanning procedures or to a breakdown of confidentiality) will be reported to the IRB immediately. We will also regularly communicate with NCCIH regarding safety monitoring practices.

8. INTERVENTION DISCONTINUATION

- **Criteria for discontinuing intervention:** A participant will be considered discontinued if they explicitly state that they would like to withdraw from the research study and cease participation in the intervention or if study staff is unable to contact the child or their guardian after 2 weeks.
- **Possible reasons for discontinuation:** Based on prior research, common reasons for discontinuing the ADAPT intervention include scheduling difficulties and the participants' lack of proximity to the medical center. It will be continually reinforced throughout the intervention that participation is optional. Families will be informed if new treatments become available. The intervention will be discontinued if a participant experiences an increase in distress and pain symptoms throughout the intervention, or if the interventionist (Barber Garcia) determines that a participant's presentation warrants more targeted care outside of what the intervention offers. Given Dr. Barber Garcia's expertise in pediatric pain psychology, she is well-suited to provide clinical oversight to make this determination. The intervention will be discontinued for all participants in the event of a study closure by the institute.
- Participation will be discontinued at any time at participant or parent request. Participants will continue to be followed with their permission if study intervention is discontinued. Should a randomized participant prematurely discontinue participation in the study, study measures and endpoints will continue to be collected if possible. Of note, based on prior research, if a participant discontinues the behavioral intervention it is unlikely that they will be retained for subsequent assessment visits. However, every effort will be made to collect endpoint and study measure data.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The stastistical hypotheses:
Aim 1. Left AMY-PFC functional connectivity will be significantly diminished (i.e., evidence of decreased hyperconnectivity) during the water load symptom provocation task (WL-SPT) post ADAPT vs. waitlist.
Aim 2. Brain activations associated with cognitive (PFC), affective (pgACC, AMY), and visceral afferent (INS, thalamus, aMCC, S1 & S2) pain will significantly be more diminished after ADAPT vs. waitlist.
Exploratory Aim. Changes in functional connectivity and brain activations following ADAPT will correspond to reductions in pain (intensity and unpleasantness) and anxiety ratings.

The choice of study design (blinded clinical trial) will enable us to answer these research questions.

Primary and secondary outcome measures are obtained from neuroimaging data. The brain regions selected have been shown in prior literature to be related to chronic pain and response to psychological intervnetions for the management of chronic pain conditons[48,71].

9.2 Sample Size and Randomization

We've used the following tool (http://neuropowertools.org/neuropower/neuropowerinput/) to conduct sample size calculations for the fMRI portion of the study. Power calculations were based on prior studies conducted by the PI's previous study mentor, who collected functional connectivity data 1) pre and post psychological therapy for pediatric pain (migraine), and 2) comparing individuals with pediatric pain (migraine) to healthy controls. While these groups are not synonymous with those proposed in the current study (which aims to compare youth with FAPD who have received psychological therapy for pain and anxiety to those in a waitlist control condition), this preliminary data yields meaningful information by which we can estimate the power required for the proposed investigation. The power calculations and sample size requirements are detailed below:

For within group changes, we relied on the pre/post data following a psychological therapy for pediatric pain (migraine). Here we found that a total sample size of 34 would be required for power of .8 and $p < 0.05$. *For between group changes*, we utilized data comparing youth with chronic pain (migraine) to healthy controls. Based on these data, a total of 35 subjects are required for power of .8 and $p < 0.05$. All comparisons were calculated using z-transformed statistical images of the whole brain, a cluster-forming threshold of $z > 3.1$ and $p < 0.05$, and a Gaussian Random Field theory-based approach for multiple comparisons. For these complex data, statistical power is defined as an 80% probability of correctly detecting an active peak for all peaks above the cluster-forming threshold. We note moderate to large effects observed for within and between group studies; thus, a total sample size of 40 ensures were are adequately powered to observe at least moderate (e.g. mean effect size difference of 0.4 or greater) effects.

Treatment Assignment Procedures

Randomization will be generated using PROC PLAN in SAS 9.3 by a biostatistician who is part of the University of Cincinnati's Center for Clinical and Translational Science and Training (CCTST). The CCTST biostatistician will not have access to the data. This data management support service will generate randomization and will assign a Treatment A/Treatment B designation. The randomization schedule and code sheet will be held confidentially by a senior Clinical Research Manager in the study mentor's (Dr. Arnetz) lab, and the study

interventionist (Dr. Barber Garcia) will contact the Clinical Research Manager to get the next assignment when a participant is enrolled in the study.

Gender and age will be used as blocking variables in randomization. Specifically, there will be four randomization tables for gender (male and female) by age (younger i.e., 11-13 years of age and older i.e., 14-16 years of age) combination:

- $11 \leq \text{Age} < 14$, Female
- $14 \leq \text{Age} < 17$, Female
- $11 \leq \text{Age} < 14$, Male
- $14 \leq \text{Age} < 17$, Male

Patients will be randomized to either ADAPT or WL. A separate randomization list will be produced for each of the four (4) blocks – Age x Sex. Per study protocol, a list of 10 treatment / control assignments will be produced per group. Within each group, a completely randomized design will be applied to allocate ADAPT or WL.

The test randomization and final randomization will require four seed numbers, one for each block size. The seed numbers below are for illustration only and will not be used.

- $11 \leq \text{Age} < 14$, Female: Seed = 111111
- $14 \leq \text{Age} < 17$, Female: Seed = 222222
- $11 \leq \text{Age} < 14$, Male: Seed = 333333
- $14 \leq \text{Age} < 17$, Male: Seed = 444444

The independent statistician will select seed numbers and will not share those final seed numbers with the project statistician (Reeves) nor other members of the project team. The randomization identification number (rand_id) will be comprised of 4 digits. The first digit will correspond to the blocks and the remaining 3 digits will be in sequential order, as listed below.

- Block 1: $11 \leq \text{Age} < 14$, Female. ID numbers 1001-1010
- Block 2: $14 \leq \text{Age} < 17$, Female. ID numbers 2011-2020
- Block 3: $11 \leq \text{Age} < 14$, Male. ID numbers 3021-3030
- Block 4: $14 \leq \text{Age} < 17$, Male. ID numbers 4031-4040

Given that other factors such as pubertal status and subjective pain levels could influence the outcome, these factors will be included in the analysis as control covariates. Each participant's exact age will be recorded at assessment allowing personnel to control for age as an additional covariate should the need become apparent during preliminary analyses.

Blinding

- **Procedure for retaining the blind.** Blinding of study personnel will be employed when possible (Table 1). Of note, our study statistician (Dr. Mathew Reeves) will only have access to subject IDs and Treatment A and Treatment B. He will generate monitoring reports for closed sessions based only on Treatment A and Treatment B. If there is an issue of serious concern

(e.g., safety issues in one arm, differential attrition etc.) that requires complete unblinding, Dr. Reeves will identify another statistician to run the unblinded reports. Dr. Reeves will also complete final analysis only by Treatment A versus B and the code will be revealed only after the data has been analyzed. Furthermore, the PI (Cunningham) will be blinded to group assignment. However, Dr. Barber Garcia will not be blinded to group assignment as study interventionist and to ensure the safety of participants and the integrity of the study. It is critical for Dr. Barber Garcia (a licensed clinical psychologist) to be aware of participants who are randomized to the ADAPT intervention in order to ensure patient safety (e.g., risk assessment for suicidal ideation, trauma/abuse, etc.) during the study. The PI (Cunningham) and study mentors (Zhu, Arnetz) will have no access to post-assessment data by group assignment until after the completion of the study.

- **Individual authorized to break the blind.** Dr. Barber Garcia will be authorized to break the blind. She will not be blinded to group assignment and therefore can determine if the study team's blind should be broken in cases where a patient's safety is in question. Dr. Barber Garcia's extensive experience as a pediatric psychologist make her appropriately equipped to manage this responsibility.
- **Circumstances for breaking the blind.** The blind will be broken at the clinical discretion of Dr. Barber Garcia. Circumstances for breaking the blind may include cases when a patient's safety is at risk, differential attrition, or if a patient's symptoms remarkably worsen throughout treatment.
- **Procedure for breaking the blind**. If the blind needed to be broken, Dr. Barber Garcia would communicate with our local IRB, any NCCIH members involved in the study, and involve our study team, included but not limited to the PI (Cunningham), co-mentors (Zhu, Arnetz), the study statistician (Reeves), and the outcome accessors.

9.3 Definition of Populations

Our intent-to-treat population (modified ITT) will be defined as those subjects who complete a post-randomization assessment.

9.4 Interim Analyses and Stopping Rules

There are no planned interim analyses. Dr. Barber Garcia will assess adherence and retention. If the treatment is deemed to be ineffective, unsafe, futile, or if there is evidence of poor study performance (e.g., slow accrual, high losses-to-follow-up, and poor quality control), a safety review may be warranted. This action would occur in consultation with the study mentors (Zhu, Arnetz), the IMC, and NCCIH. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. Such findings are presented to the study statistician (Reeves) or to the IMC statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his

findings to a closed session of the IMC or to the Safety Officer and/or NCCIH. The findings are used to determine what steps will be taken.

9.5 Outcomes

9.5.1 Primary Outcome

Subjects will first complete localizer sequences for targeting of other series. A B0 field map (B = magnetic field) will be used to correct for distortion due to susceptibility artifacts. A high resolution T1 weighted anatomical volume will be obtained to provide a detailed view of brain anatomy. Functional connectivity will be examined using the Blood Oxygenation Level Dependent (BOLD) effect.

9.5.2 Secondary Outcomes

Brain activation during the WL-SPT will be assessed by arterial spin labeling (ASL). In order to examine relationships between resting brain activity and other variables, cerebral blood flow (CBF) will be measured in a quantitative fashion via ASL, which is the optimal for assessing steady-state conditions. Nine series will be obtained (5-10 mins each): Pre-WL-SPT: 1 MPRAGE; 2 resting ASLs; 2 resting BOLDs; post-WL-SPT: 2 ASLs; and 2 BOLDs.

9.6 Data Analyses

For fMRI analysis, image processing and data analysis will be accomplished by FSL software. Each subject's functional images will be registered to their structural data using a six-parameter linear 3D transformation and then nonlinearly warped to standard space (MNI152). Analyses of both BOLD and ASL data will be accomplished via mixed effects ANOVAs. Data will be coded prior to analysis to conceal patient status to ensure blinding.

Clusters of activation will be identified using a threshold of $Z > 3.1$ and statistical significance will be estimated according to Gaussian random field theory. Functional connectivity analysis will be conducted (Aim 1) to identify changes in functional connectivity between the AMY-PFC in ADAPT completers vs. those in the waitlist condition. A seed to whole brain analytic approach will be used to identify any/all differences observed. Pain-related brain activations are expected to diminish for those that complete ADAPT compared to the waitlist condition (Aim 2). For the exploratory aim, mechanisms associated with a positive treatment response (decreased pain intensity/ unpleasantness/ anxiety during WL-SPT) after ADAPT will be identified. Normalization of abnormal connectivity patterns are predicted to categorize changes in pain and anxiety. Specifically, decreases in brain activations and reductions in functional connectivity will be examined in relation to improvements in pain and anxiety post treatment using multiple (linear) regression.

While all efforts will be made to minimize missing data through the use of electronic data capture and real-time adherence data collection, missing data is still inevitable in RCTs. Thus, we will employ several strategies to handle missing data with specific attention on how to handle missing not-at-random. Specifically,

missing data will be handled via ML estimation with auxiliary correlate inclusion (e.g., Graham, 2003; Enders, 2010). Missing not at random will be addressed with mixture MNAR methods (e.g., Gottfredson, Bauer, & Baldwin, 2014; Muthen, et al., 2011; Sterba & Gottfredson, 2015).

Given that other factors such as pubertal status and subjective pain levels could influence the outcome, these factors will be included in the analysis as control covariates. Each participant's exact age will be recorded at assessment allowing personnel to control for age as an additional covariate should the need become apparent during preliminary analyses.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Standardized, validated measures used in prior pediatric pain studies will be used (*6.1 Schedule of Evaluations)*. These measures will be administered using the REDCap platform. Participants and caregivers will be given the option to either complete baseline and post-assessment measures during their respective baseline/post assessment visit or before this visit using their own electronic device (to reduce the length of the in-person visit). A blinded post-baccalaureate research coordinator will serve as the outcome assessor and collect data at assessment visits. Home practice during ADAPT will also be measured (online module completion). Should a randomized participant prematurely discontinue participation in the study, study measures and endpoints will continue to be collected if possible. Any concomitant interventions (i.e., medical and psychological) experienced by the participants (either allowed or prohibited) will also be assessed for and recorded at baseline and post assessments. Participants will provide the reason and duration of concomitant interventions at the baseline and post assessment visits.

To ensure confidentiality, identification numbers will be used on data collection forms in lieu of names. Regarding the use of online measures and web modules, material development will be conducted in accordance with MSU policies. Hardware for this study will be provided and maintained by MSU Informatics, which maintains a secure server for supporting projects that potentially contain protected health information (PHI) and are subsequently subject to compliance with federal and state regulations regarding data of this type. The data obtained from the web program will be stored on the server, which will be backed up regularly.

10.2 Data Management

All data will be identified with ID numbers exclusively and kept in locked files in a space in the Secchia Center or on a secure computer that is designated specifically for the purposes of this project. All de-identified data (with the exception of fMRI data) will be saved into REDCap, a password-protected database. Data output will be stored on a network devoted solely to the research activities associated with MSU's Biomedical Research Informatics Core (BRIC). In order to assure the accuracy of data entry, data will be verified in real-time by study staff via database-incorporated data entry checks. Electronic data stored on MSU's network is backed up nightly. The

server is maintained and all backups are conducted by the BRIC. The fMRI data will also be stored on a secure server, backed up nightly, and will only be accessible to study staff.

10.3 Quality Assurance

10.3.1 Training

To ensure protocol integrity, staff training will include required human subjects training, GCP training, and study/intervention specific training. Study staff training will vary based on roles (i.e., interventionists will receive specific training on conducting the intervention from the PI).

10.3.2 Quality Control Committee

N/A

10.3.3 Metrics

N/A

10.3.4 Protocol Deviations.

All deviations will be reported to the IRB for review. They will also be recorded using a protocol deviation form documenting a brief description of the deviation, the number of participants who experienced a given deviation, and a summary of the action taken in response to the deviation or group of similar deviations. All protocol deviations will also be documented in a protocol deviation log.

10.3.5 Monitoring

The study team will have quarterly meetings to monitor the progress of the study, the integrity of the treatment, discuss the need for any protocol refinements, and conduct regular safety monitoring checks of adverse events and unanticipated problems.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed assent and consent documents and any subsequent modifications will be reviewed and approved by the MSU IRB.

11.2 Informed Consent Forms

A signed assent and consent form will be obtained from each participant and their legal guardian (e.g., person with power of attorney) before completing any study activities. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it

prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the forms will be given to the legal guardian.

All efforts will be made to ensure that youth and their families understand the study and the associated risks and benefits. Participants will have opportunities to voice questions/concerns before formally providing consent/assent. Non-English speakers or those with cognitive delays that would limit understanding of the consenting process will be excluded from participation in the study.

11.3 Participant Confidentiality

There is a minimal risk that the data collected for each participant may be viewed by individuals outside the research team. To minimize risk to confidentiality, every effort will be made to ensure that research data are kept confidential and stored so that data cannot be accessed by individuals who are not part of the research team. Unique identification numbers will be assigned to participants, and all case report forms will be coded with this number rather than a name. A password-protected master list linking the identification number to participant names will be stored on a secure computer separate from the study data. Access to the master list will be limited to key study personnel. Upon study completion, all study materials and participants' personal information will be destroyed, with the exception of recordings retained for training purposes. Locked filing space within the Secchia Center will be identified and used exclusively for the purposes of this study.

All consent forms, contact information and identifying data will be stored either in a secure location within the Secchia Center or on a secure computer. The subject codebook will be stored separately in a password protected document. Before they begin the study, participants and parents will be informed about the importance of confidentiality.. Regarding the use of online measures and web modules, material development will be conducted in accordance with MSU policies. Hardware for this study will be provided and maintained by MSU Informatics, which maintains a secure server for supporting projects that potentially contain protected health information (PHI) and are subsequently subject to compliance with federal and state regulations regarding data of this type. The data obtained from the web program will be stored on a secure server, which will be backed up regularly.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

N/A

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

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