PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Janet Wozniak, MD

PROTOCOL TITLE
An Open-Label Clinical Trial Conducted via Telepsychiatry of Complementary and Alternative Treatments (Omega-3 Fatty Acids and Inositol vs. N-acetylcysteine) for the Management of Emotional Dysregulation in Youth with Non-verbal Learning Disability (NVLD) and/or Autism Spectrum Disorders (ASD)

FUNDING
Sponsored by Demarest Lloyd, Jr. Foundation

VERSION DATE
Version: AME 29
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SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

The purpose of this study is to examine the relative effectiveness of omega-3 fatty acids plus inositol versus N-acetylcysteine (NAC) in reducing symptoms of emotional dysregulation in children and adolescents (ages 5-17) with non-verbal learning disability (NVLD) and/or autism spectrum disorders (ASD). We hypothesize that omega-3 fatty acids plus inositol combined intervention will result in improved outcomes relative to using NAC as monotherapy.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Emotional dysregulation affects a sizeable minority of children with non-verbal learning disability (NVLD) and related conditions such as autism spectrum disorders (ASD). The occurrence of a mood disorder in these children and adolescents further compromises their problematic course and outcome. Unfortunately, none of the current conventional treatments for mood disorders can claim a high level of efficacy combined with easy tolerability in all individuals. Increasingly, clinicians, researchers, and patients and their families are turning to natural products considered

complementary and alternative treatments. Yet, few studies exist to support the use of these dietary supplements in pediatric populations.

Omega-3 fatty acids (including EPA and DHA) are important components of cell membranes and are important for cell-to-cell communication in the brain. However, abnormalities in fatty acid composition of phospholipids in cell membranes have been described in psychiatric disorders in general and in bipolar disorder in particular (Horrobin & Bennett, 1999; Horrobin, Glen, & Vaddadi, 1994; Peet, Murphy, Shay, & Horrobin, 1998; Stoll et al., 1999). With reduced omega-3 fatty acids, the fatty acid composition of the cell membrane phospholipids would be altered, possibly leading to altered neurotransmitter binding and psychopathology. Thus, supplementing omega-3 fatty acids is suggested to have a potentially therapeutic role in the management of mood disorders.

Inositol is a precursor for, as well as a product of, the phosphatidylinositol (PI) cycle and is therefore common and widely found, located primarily within cell membranes (Baraban, Worley, & Snyder, 1989). Although the mechanism of action of inositol remains unclear, we can indirectly presume from the available evidence that subjects with mood disorders experience a decrease in brain myo-inositol, which adversely affects the functioning of the PI second messenger system, which in turn results in mood changes. Dietary supplement with inositol, therefore, could improve the functioning of the PI system and treat depressive symptoms.

N-acetylcysteine (NAC) is an acetylated amino acid and a precursor of glutathione that acts as an antioxidant in the brain to reduce oxidative stress, which has been implicated in bipolar disorder and major depression (Magalhaes et al., 2011). The main interest in psychiatry involves NAC as a precursor to glutathione, which acts as a potent antioxidant diminishing free radicals that can lead to cell damage and death. Glutathione is a major endogenous antioxidant in the brain. Glutathione is a molecule comprising three peptides: glutamate, cysteine, and glycine. The addition of the cysteine is the rate-limiting step, and NAC provides this key substrate for the creation of glutathione.

Recent work by our group has shown improvements in emotional dysregulation in youth using omega-3 fatty acids (Wilens et al., 2017; Wozniak et al., 2007) and an even more robust outcome when combining omega-3 fatty acids with inositol (Wozniak et al., 2015; Wozniak et al., 2016). Work by our group also suggests that N-acetylcysteine (NAC) is helpful in the management of emotional dysregulation in youth. However, these studies are not directly comparable as they were conducted at different times with different study clinicians and age groups.

Additionally, a major limitation of the previous clinical trials by our group on the efficacy of natural supplements is the burden on families incurred by travel to appointments. In our previous clinical trials, recruitment, retention, and patient satisfaction were all negatively impacted by the need to come into the office for study visits. Telepsychiatry is an established and rapidly growing initiative in the Department of Psychiatry at MGH. Dr. Wozniak has lead the department in using virtual visits to connect with patients and provide clinical psychiatric care. She has personally championed the use of virtual visits with the autism spectrum population, for whom the adverse sensory experience of a hospital visit is especially burdensome.

Since omega-3 fatty acids, inositol, and NAC are safe with nor serious associated adverse events, studies of these treatments are well suited to virtual visits. Our preliminary data with all three supplements demonstrated minimal adverse events and no medical safety events. Therefore, this study is proposed to examine the relative effectiveness of omega-3 fatty acids and inositol versus NAC using telemedicine to conduct study visits. This will allow for a comparison of these natural supplements for the treatment of emotional dysregulation while providing subjects and their families with a more convenient and pleasant experience, which will most likely positively impact both recruitment and subject satisfaction and retention.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This will be a 6-week, open-label, randomized clinical trial study to compare efficacy and tolerability of the natural treatments omega-3 fatty acids, inositol, and NAC in the treatment of mood dysregulation in children and adolescents with NVLD/ASD. Subjects will include youth ages 5-17 years with a non-verbal learning disability (NVLD) or autism spectrum disorder (ASD) and current symptoms of emotional dysregulation. We will enroll 60 subjects to allow for the randomization of 30 subject into each treatment arm.

The full inclusion and exclusion criteria are included below:

A. Inclusion Criteria:

1. Male or female subjects, 5-17 years of age.
2. A previous established diagnosis of non-verbal learning disability (NVLD) or DSM-V Autism Spectrum Disorder and/ or combined T-scores on the Child Behavior Checklist $\geq$ 195 on the Withdrawn + Social Problems + Thought Problems subscales.

3. Current symptoms of emotional dysregulation as indicated by combined T-scores on the Child Behavior Checklist $\geq$ 180 on the Anxiety/Depression + Aggression + Attention subscales.
4. Subjects and their caregivers must be English-speaking and have a level of understanding sufficient to communicate intelligently with the investigator and study coordinator, and to cooperate with all tests and examinations required by the protocol.
5. Subjects and their caregivers must be willing and able to comply with all study procedures.
6. Each subject and his/her authorized legal representative must understand the nature of the study. The subject's authorized legal representative must sign an informed consent document and the subject must sign an informed assent document.
7. Subject must be able to swallow pills.
8. Subject must have access to a computer with a camera, speaker, microphone, and internet connection.
9. Subjects must be willing to refrain from treatment changes during the study protocol.

B. Exclusion Criteria:

1. Investigator and his/her immediate family; defined as the investigator's spouse, parent, child, grandparent, or grandchild.
2. Serious or unstable illness including hepatic, renal, gastroenterological, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease.
3. History of bleeding diathesis, including those with von Willebrand disease.
4. Uncorrected hypothyroidism or hyperthyroidism.
5. History of sensitivity to omega-3 fatty acids, inositol or NAC. A non-responder or history of intolerance to omega-3 fatty acid, inositol or NAC after 2 months of treatment at adequate doses as determined by the clinician.
6. Severe allergies or multiple adverse drug reactions.
7. Unstable or untreated seizure disorder.
8. DSM-IV substance use, abuse or dependence.
9. Judged clinically to be at serious suicidal risk for C-SSRS score ≥ 4.
10. Current diagnosis of schizophrenia.
11. Current diagnosis or symptoms of psychosis.
12. IQ < 70.
13. Pregnant or nursing.
14. Weighs less than 12.5kg.

The main outcome measures will be improvement in manic symptoms as measured by the Parent-Young Mania Rating Scale (P-YMRS) and improvement in depressive symptoms as measured by the parent-completed Children's Depression Inventory (CDI) scale.

Only subjects who are not responding to their current treatment regimen will be recommended to taper from their medications. No subject on a useful treatment will be recommended for taper from medication for entry into this study. Subjects and their current treating prescriber may opt to continue with current treatment even if taper is recommended. Typically, a 7-day washout period is recommended for antidepressant medications and atomoxetine (with the exception of Prozac requiring 14 days). Mood stabilizers/atypical antipsychotics are generally washed out over the course of 7 days, while stimulants are discontinued in 3 days. Discontinuation of medications will be done in consultation in the prescribing clinician.

We plan to treat subjects with the following doses:

Omega-3 Fatty Acids
All subjects: 1020mg QAM + 1020mg QPM
+
Inositol
Subjects under 25kg: 1000mg daily
Subjects weighing 25kg or more: 2000mg daily

OR

NAC:
Effervescent Tablets
Subjects ages 5-12: 1800mg daily
Subjects ages 13-17: 2700 mg daily
Capsules
Subjects ages 5-12: 1800mg daily
Subjects ages 13-17: 2400mg daily

At each visit, measures of safety and effectiveness will be obtained using rating scales.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Interested parents/guardians will first complete a phone screen with the study coordinator or a research assistant. If the child meets eligibility criteria based on the phone screen, the parent/guardian will be asked to complete the Child Behavior Checklist (CBCL) via RedCap, a secure online data capture system. The parent/guardian will be provided with an online consent statement and asked to indicate their agreements to participate in the online questionnaire portion of the study before they are brought the CBCL.

If a parent/guardian has completed pre-screening procedures for another research study or the clinic in our department within the past 3 months, they will not be asked to complete that procedure again, and the data collected previously will be used for pre-screening for this protocol.

Subjects deemed to be eligible following the phone screen and completion of the CBCL will either be scheduled for an in-person visit at our office or, during the COVID-19 pandemic, to speak with a study clinician via phone to obtain informed consent prior to completing further screening and baseline study procedures via virtual visit. Informed consent will be obtained from all subjects and their legal guardian at the initial in-person visit or, during the COVID-19 pandemic, during a phone call with a study clinician. The subject's legal guardian will then answer questionnaires regarding current medications and demographic details. They will also complete the BRIEF, SRS, P-YMRS, and CDI questionnaires. A study clinician will complete the Columbia Suicide Severity Rating Scale (C-SSRS) to assess past and current suicidality and self-harmful behaviors; conduct an observational mental status exam; record baseline severity scores of Clinical Global Impression (CGI) for mania, depression, and overall bipolar disorder; and will review current medications and recommend any medication taper. A trained member of study staff will obtain and record height and weight for all subjects. A urine pregnancy test will be conducted for all female subjects who have reached menstruation. If the test is positive, the subject will not be able to participate in the study and she will be informed of the results, along with her parent/guardian if she agrees. Even if she does not agree, the study doctor may still decide, based on the subject's age, maturity, or medical condition, to inform the parent/guardian.

In the case that it is deemed necessary at the in-person screening/baseline visit (i.e. if a subject has plans to make changes to concomitant medications or cannot begin active participation in the study at the time for some other reason), the subject will be allowed to enroll in the study and complete study tasks that require the subject to be in the office at that time and to complete all other tasks that can be completed remotely at a later date, without returning to the office.

During the COVID-19 pandemic, the screening/baseline visit will be conducted remotely. Revised timeline: parental consent and child assent → dispensation of study medication → week 99/0 tele-visit. After consent has been obtained, the study medication will be mailed to the subject. Once the subject has received the study medication by mail, the subject and their parent(s)/guardian will complete a tele-visit with a study clinician in order to complete all study procedures requiring a clinician. All typically completed clinician assessments/rating scales can safely and effectively be completed remotely during the tele-visit with the study clinician and the subject and their parent(s)/guardian. The study coordinator will also complete a phone

call with the subject and their parent(s)/guardian on the same day as the tele-visit with the study clinician in order to complete the following procedures. Parents/guardians will be asked to self-report height and weight. It will be noted that these measurements were provided by a parent/guardian report rather than study staff measurement. For any female subjects who have begun menstruation, a pregnancy test will be ordered using study funds and sent directly to the subject's home address. The test will be ordered in advance to ensure delivery before the week 99/0 tele-visit. The study coordinator will review the procedure for completing the urine pregnancy test while on the phone and have the subject complete the test while remaining on the line. The subject/subject's parent or guardian will verbally report the result to the study coordinator, and will also send visual confirmation (i.e. a photo of the test with results send via secure email) prior to beginning the study treatment. Finally, the study coordinator will send an email link to the parent(s)/guardians to complete a battery of assessments/rating scales via REDCap. All typically completed parent assessments/rating scales can safely and effectively be completed remotely. These assessments/rating scales are already approved to be completed via email link to REDCap for the week 1-6 tele-visits.

At each following weekly tele-visit, parents will indicate adherence to the study treatment, list any new concomitant medications, and complete questionnaires regarding symptoms of emotional dysregulation, mania, and depression. A study clinician will also complete the C-SSRS to monitor suicidality and self-harmful behaviors, record CGI (Severity and Improvement) scales for mania, depression, and overall bipolar disorder, record any side effects or adverse events, and review and confirm parent-reported information.

At endpoint, parents will report current weight and complete the BRIEF and SRS questionnaires in addition to the weekly questionnaires.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Families with children and adolescents with NVLD/ASD and emotional dysregulation can speak with their primary care doctor to obtain a prescription for medication to treat mood disorders or receive a referral to a specialist. Available medications for treating severe mood problems in children include atypical antipsychotic medications and mood stabilizers and in some cases antidepressants. The study doctor can discuss the risks and benefits of other treatments with potential participants and their parent/guardian prior to enrollment.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

All efforts are made to minimize risks to subjects. The protocol is designed to ensure that safety measurements are completed prior to study drug treatment and that the subject's response to study drug is closely monitored. Previous studies by our research group confirm that these study treatments are safe for use in children at these doses. All procedures used in this study are consistent with sound research design and do not unnecessarily expose subjects to risk. Clear drop criteria will be employed, as described below.

We will be using secure Partners workstations to access Vidyo, a videoconferencing platform, in combination with Skills Based Routing (SBR), a patient management software, to conduct the weekly study visits. Both Vidyo and SBR are secure mediums. Partners Information Systems and MGH Health Information Services have already approved this technology for use.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Each week, a study clinician will record any adverse events.

Poor response to treatment, leading to drop from the study, will be measures by a CGI-bipolar score that is 2 points higher (more severe) than baseline for more than 2 consecutive weeks or a P-YMRS score that is 30% higher than baseline for more than 2 consecutive weeks only if the P-YMRS is in a clinically significant range of >15. If a subject should score a 4 or higher on the C-SSRS, he or she will be dropped from the study. The study clinician will assess the level of risk and take appropriate actions, including an immediate referral to emergency services.

In addition, drop from the study will occur at clinician discretion for worsening of clinical course, non-compliance with treatment, or inability to tolerate study treatment.

Subjects who fail to keep study appointments or are non-complaint (less than 70% compliance for 2 weeks or longer) may be dropped from the study. If a subject becomes pregnant or is found to be abusing substances during the study, he or she will be dropped from the study. These study subjects will be given a referral for local treatment.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Potential side effects are few and will be monitored for throughout the research study. Consent forms will clearly list potential treatment side effects. Since they are natural products, it appears that omega-3 fatty acids, inositol, and NAC have a low potential for unwanted side effects or negative effects on the child's growth and development. It should also be noted that no important toxic effects have been reported in previous use in humans and animals.

The treatment omega-3 fatty acids has been used and studied in pediatric populations with few side effects. The most common side effects reported with use of omega-3 fatty acids are upset stomach and complaints of a fishy taste. Other side effects include nausea, skin rashes, decreased platelet aggregation, bleeding tendencies, and increased restlessness.
Inositol is a safe, natural diet supplement with emerging evidence of utility in psychiatric populations. The most common side effects include mild clinically insignificant increases in glucose, flatus, nausea, sleepiness and insomnia, dizziness, headache, and diarrhea.

The most common side effects reported with use of NAC are gastrointestinal. Other less common side effects that have been reported include fatigue, nervousness, vivid dreams, heartburn, pruritus (without rash), and headaches (Berk et al., 2008; Ghanizadeh & Moghimi-Sarani, 2013; Gray et al., 2012; Hardan et al., 2012; Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007). Serious side effects are uncommon.

Answering detailed questionnaires may create a mild degree of inconvenience or emotional upset for the subjects. The PI will be available to respond to any concerns or to answer other questions about the study (available by pager 24 hours per day). All of the information about participants will be treated confidentially. Subjects may refuse to answer any of these questions.

Having treated hundreds of bipolar patients, we are aware that this is a group of very highly disturbed children at risk for psychosis, suicide and disruption in the family. Although it is unlikely that these risks will be exacerbated by the protocol, we will be vigilant regarding the potential for patient decompensation or dangerousness to self or others. In the execution of research protocols, our primary concern is always the safety of the research participant. Given the especially unstable nature of bipolar patients, we will be available to the study staff and to handle clinical

emergencies with patients and their families. The PI has a beeper and is available for emergencies 24 hours per day. The Massachusetts General Hospital has an active and well-staffed psychiatric emergency service that will be available to subjects if needed. This study has clearly defined exit criteria to ensure the safety of participants. Dr. Wozniak has treated hundreds of bipolar patients via tele-psychiatry and is aware of how to assist in the event of a crisis with call to 911 and local police.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

There may be no direct benefit to the subjects participating in this trial. Potential benefits to the subjects include rapid access to treatment, free psychiatric assessment, and a free trial of potentially useful treatments with low associated risks, and the opportunity to contribute to medical science and thus help others with the same disorder(s).

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

We do not include pregnant or nursing women due to the unknown effects of study treatments on fetuses and infants. We do not involve prisoners or institutionalized individuals in our studies. Those who are economically or educationally disadvantaged, hospital employees, or patients from medical practices of the investigators are eligible to participate in our studies provided that they meet inclusion and exclusion criteria. Females and minorities are also welcome to participate as study subjects, provided that they meet inclusion and exclusion criteria.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Subjects who do not understand English cannot participate in our studies, for the study requires that subjects and their parents be able to verbally

communicate with the clinicians during the weekly completing of rating scales. The assessment instruments are not available and have not been adequately standardized in other languages. If available, adding the complexity of a translator has the potential to make the subject experience exhausting.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

We will use advertisements on the Internet, including advertisements posted on the Partners Clinical trials website, and flyers to recruit participants. Individuals who respond to advertising will go through a phone screen with the study coordinator or research assistant via phone and will then be screened by a study clinician.

Participants may also be recruited from the referral pool of existing and new patients in the Pediatric Psychopharmacology Program and the MGH Child Psychiatry Outpatient Clinic, from the pool of children screened for participation in Protocol #2019-P-000846 ("An Open-Label Clinical Trial Conducted via Telepsychiatry of Complementary and Alternative Treatments (Omega-3 Fatty Acids and Inositol vs. N-acetylcysteine) for the Management of Emotional Dysregulation in Youth"), or via advertising in the local media. Clinicians may introduce the study to appropriate patients and their parent/guardian and provide those who may be interested in participating with the study coordinator's contact information. The patient and their parent/guardian may then contact the study coordinator for more information about the study and to be screened for eligibility over the phone. Prospective subjects and their parents/ guardians will not be contacted by research staff unless they have given explicit permission to be contacted for research.

All subjects that enter the study will undergo standard screening and diagnostic procedures.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital,

parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subjects will be provided with omega-3 fatty acids, inositol, or NAC as appropriate at no cost. Subjects can be reimbursed for parking at MGH for the initial in-person visit.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Informed consent and assent will be obtained prior to performing any protocol procedures and prior to administration of study treatment. The informed consent and assent documents will be used to explain in simple terms the risks and benefits of study participation to the subject and his/her parents/guardians. The nature of the study will be fully explained to the subject and his/her parents/guardians by a board-certified physician who is either the primary investigator or co-investigator. The subject and his/her parents/guardians will be encouraged to ask questions pertaining to their participation in the study, and they may take as much time as they feel necessary to consider their participation, as well as consult with their family members or physician. Participation in this study is voluntary and the subjects may withdraw from the study at any time.

Assent for adolescents ages 14-17 will be documented on a separate line of the parent/guardian consent form. Assent for children ages 7-13 will be documented on a separate assent form that describes the study in age-appropriate language. Subjects who turn 18-years-old during the trial must

re-sign on a designated line on the parent/guardian consent form when they reach the age of maturity.

Should a subject be enrolled from a clinician's own patients, the subject will be offered the opportunity to take as much time as they feel necessary to review to consent form at their convenience and consider their participation in the study. Study staff will be available to contact if potential subjects have any further questions about the study and consent. All subjects recruited from among the investigator's own patients will be offered the opportunity to discuss participation with a physician colleague before deciding whether or not to participate. In this case, the investigator will also reinforce that participation in voluntary and the decision not to participate will not affect their care, now or in the future.

During the COVID-19 pandemic, informed consent will be obtained remotely. This may be done in 2 ways:

1. Using Adobe eSignature: Study staff will send the consent form and assent form (when applicable) to subjects in PDF form ready for Adobe eSignature via email with a brief statement (email template submitted) explaining why they are receiving this form and further instructions. Study staff will schedule a time for the subject and their parent(s)/guardian to meet with a study clinician via phone to complete consent. The study clinician will have a conversation by phone with the subject and their parent(s)/guardian to obtain consent in the usual fashion: review the consent form, review inclusion and exclusion criteria, review risks and benefits of the study, review alternatives to participation, and answer any questions subjects and their parent(s)/guardian may have. If the subject and their parent(s)/guardian decide to participate, they will sign the consent form and assent form (when applicable) using Adobe eSignature. The study clinician will also sign the consent form using Adobe eSignature prior to beginning any study procedures. Subjects will be sent a copy of the signed form by email for their records.
2. Mailing a physical copy of forms: Study staff will send the consent form and assent form (when applicable) to subjects via mail or secure email along with a brief letter explaining why they are receiving this form and the phone number to call once they receive it. Study staff will schedule a time for the subject and their parent(s)/guardian to meet with a study clinician via phone to complete consent once they receive the forms via mail or email. The study clinician will have a conversation by phone with the subject and their parent(s)/guardian to obtain consent in the usual fashion: review the consent form, review inclusion and exclusion criteria, review risks and benefits of the study, review alternatives to participation, and answer any questions subjects and their parent(s)/guardian may have. If the subject and their parent(s)/guardian decide to participate, they will sign the consent form and assent form

(when applicable) and mail it to the study clinician, who will also sign the consent form prior to beginning any study procedures. Subjects will be sent a copy of the signed form by secure email for their records.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Study monitoring will include periodic inspection of all documents at regular intervals by the Principal Investigator and members of study staff. Such documents will include diagnostic testing, evaluations, progress notes, copies of medication test results, and written informed consent forms. The PI is responsible for monitoring safety and data.

A subject may discontinue from this trial at any time, whether it is due to adverse effects or disinterest. All procedures have been designed to minimize subject discomfort and no subject will be asked to engage in research procedures not outlined in the consent form.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include

the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

The Principal Investigator and the project medical staff will be available 24 hours per day via pager to respond to all reports of adverse events, including those that emerge outside of regularly scheduled visits.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The Principal Investigator will meet weekly with study staff to address procedural issues and the coordinator will audit each subject's binder within a month of his/her completion of the study. Co-investigators are actively involved in the monitoring and quality assurance of these trials. These periodic quality assurance audits will ensure accuracy and completeness of all medical records, IRB files and correspondence, and the informed consent documentation.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Subject information collected during the study will be kept confidential by the study doctor and staff and will not be made publicly available unless disclosure is required by law. Subjects will be assigned code-names and ID numbers. Only study staff and co-investigators will have access to the information linking subjects to their ID numbers. Information will be held and processed on a computer. Access to these computerized records will be password protected and restricted to study staff.

Data will be collected using RedCap, an electronic data capture system that streamlines data collection and management and ensures data integrity. RedCap software allows researchers to design and implement study surveys for collection, storage, retrieving, and manipulating data electronically. Subjects and their guardians will enter survey responses into electronic assessment forms, using personal computers. Study staff will use terminals at the research site or encrypted computers. The responses will then be transmitted securely via an encrypted connection and stored in a secures database. Electronic data capture obviated the need for subsequent data entry by staff, thus minimizing human error. Data will be collected on paper versions of scales or assessments and entered manually if the electronic data capture system, RedCap, is not functioning properly.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

N/A

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw

their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

N/A

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

N/A