PQXNIH2- Protocol & Data and Safety Monitoring Plan

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Study Overview

PainQx is currently engaged in the second phase of a two phase NIDA sponsored project entitled "Development of a Clinical Tool Utilizing an EEG-Based Algorithm for the Objective Quantification of Pain" funded under FOA Number PA-16-302 Omnibus Solicitation of the NIH, CDC, FDA, and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]).

In Phase I of the project, PainQx demonstrated that 19 lead EEG data can be used to detect changes in brain activity when a patient is in pain and produced a biomarker that scales with the intensity of chronic pain the patient is reporting via the Numeric Rating Scale (NRS) 0-10 scale.

The primary purpose of this study is to demonstrate that the relationship between the NRS and a QEEG based biomarker demonstrated using 19 lead research oriented EEG systems can be replicated using a lower cost, portable EEG recording device that can be set up quickly by a non-specialist thereby significantly improving clinical utility of the ALGOS platform. The targeted EEG recording device for use in the study will also be used for the FDA Validation Trial and initial commercial product launch, thus this study will serve as an FDA Beta in addition to supporting achievement of the NIDA Phase II objectives.

Phase II Research Strategy

Phase II Hypothesis

The relationship between the NRS and a QEEG based biomarker demonstrated using 19 leads can be demonstrated using a commercially available EEG recording device that can be set up by a non-specialist in less than 10 minutes, thereby significantly improving clinical utility.

Specific Aim 1

Select an EEG recording device and transition the developed software modules to work with the selected EEG recording device.

Specific Aim 2

Optimize the PainQx algorithm and demonstrate performance using the selected EEG recording device from Phase II Specific Aim 1.

Power Analysis

The performance achieved as part of Phase I of the NIDA study was used to estimate the minimum number of subjects required for Phase II. Because of the potential for performance degradation and/or the need to perform statistical analysis on subsets of the data (e.g. performance for each pain etiology included in the study, additional enrollment is planned beyond the minimum number of subjects indicated by the power analysis.

Inclusion and Exclusion Criteria

Subjects

Two hundred fifty (250) male and female pain patients with symptoms in excess of 3 months duration (per the IASP definition of Chronic Pain) between the ages of 18-85 years will be enrolled in this phase of the study. Fifty (50) healthy normal subjects between the ages of 18-85 years will also be enrolled. The normal subjects are added to assure that the study spans the entire pain scale including those with an NRS of 0. Subjects who meet inclusion/exclusion criteria will be asked to volunteer for the study and to provide written informed consent. Subjects will receive a fee for participation to reimburse them in part for their travel and time.

Defining Chronic Pain (CP)

For this study, we will apply the guidelines of the International Association for the Study of Pain (IASP). IASP defines chronic pain as "pain which has persisted beyond normal tissue healing time, taken, in the absence of other criteria, to be 3 months or greater". The IASP definition is most widely applied in published studies, although it is noted that severity, disability, and impact on daily life and mood are not considered in this definition. Therefore, to supplement the IASP guidelines, we have added measures of each of these dimensions in the clinical self-report forms to further characterize patients within the group (see below).

Inclusion Criteria, Pain Patients

- Male and female chronic pain patients
- Patients between the ages of 18-85 years
- Patients exhibiting the presence of symptoms in excess of 3 months duration
- Patients suffering from neuropathic (e.g., lower back pain), osteoarthritis, or muscular skeletal pain
- Patients with evidence of pathology related to the painful condition on which diagnosis was made (e.g., results of imaging or diagnostic pain code)
- Patients with NRS pain scores across the full range (1-10) at the time of testing

Inclusion Criteria, Normal (no-pain) Group

- Subjects will be included with no history of pain with a duration of greater than 3 months, and no report of pain at the time of testing (or within 3 months of testing)

Exclusion Criteria

- Patients with medically diagnosed psychotic illness
- Patients with medically diagnosed drug or alcohol dependence in the past 12 months
- Patients with a medical history of head injury with loss of consciousness and amnesia (within the last 2 years)
- Patients with skull abnormalities that preclude the proper placement of the electrodes for the EEG data acquisition
- Patients who have a spinal cord stimulator, or other implantable devices
- Patients for whom the source of pain at the time of the evaluation is associated with: neurological disorders (multiple sclerosis, Parkinson, dementia), diabetes, migraines, or those with reflex / sympathetic dystrophy disorder/complex regional pain syndrome, fibromyalgia, or visceral pain

Note: This does not exclude patients who suffer from these disorders if the current source of pain is not due to the disorder. For example, patients with diabetes are NOT excluded, but patients whose pain at the time of the evaluation is a result of diabetic neuropathy are excluded. Similarly, patients with a history of migraines but for whom a migraine is not the current source of pain at the time of the evaluation are NOT excluded.

- Patients with cancer
- Patients on workers compensation or disability
- Patient on anticonvulsant medication
- Patients who have a history of seizures

All patients meeting inclusion/exclusion criteria and who provide written informed consent will be enrolled in the study.

Analgesic medication prescribed for a candidate patient's pain condition will be allowed in the following categories: oral and transcutaneous narcotics, tricyclic antidepressants, SNRIs, anticonvulsants, non-steroidals, and corticosteroids.

Trial Management

Target Population Distribution

While both genders will be sampled, the sample will be a convenience sample of patients present to the offices of the referring physicians. There are no plans to control for gender, but the convenience nature may impact gender balance of the sample. It is expected that gender will be approximately 50-50 in this sample.

Likewise, it is expected that race and ethnicity will be proportional to the reported incidence of chronic pain within the patient population of the practices and programs from which the subjects were referred. The quantitative EEG methods that will be used in this study and the location and activation of brain regions of interest in a chronic pain state have been determined to be culture, ethnic and gender neutral, so strict control of these study variables is not considered a requirement.

Data Management & Analysis

Data Acquisition

Equipment & EEG Acquisition

For the initial 100 participants, PainQx will be providing one or more EEG headsets and EEG data collection devices from BioSignal Group to be used to collect subject neural activity. Following the intial collection period, PainQx will provide EEG headsets and collection devices from Zeto, Inc.

Fifteen (15) minutes of eyes-closed resting EEG will be recorded with the device placed in accordance with the International 10/20 Electrode Placement System, referenced to linked earlobes. In this phase of the study, the 15 minutes of EEG data collected will be divided into two segments with the first 10 minutes used to extract 2 minutes of artifact-free data, and the additional 5 minutes of data used for demonstration of replicability. ECG data will also be collected during the period of acquisition using the Zeto, Inc device. Patients will be monitored for vigilance during EEG and ECG recording.

i. All electrode impedances will be below 10,000 Ohms.
ii. The EEG amplifiers will have a bandpass from 0.5 to 80 Hz (3 dB points), with a 60 Hz notch filter. Data will be sampled at a rate of 500 samples/sec with 24-bit resolution.
iii. Patients will be monitored for vigilance during EEG recording.

Collection of Subject Self-Rating and Pain Scales

The following self-rating scales will be used to provide critical data on severity, disability, mood, and neuropathy, as well as relevant patient history. It is recommended that the patient survey information be collected as the EEG is being set up on the patient to reduce the total time required

for the clinical study. A brief training video will be shown to the patient before the survey begins. This video describes the test, good practices during the test, and description of NRS.

i. Brief Pain Inventory (BPI): This is used to rate overall pain, current pain and maximal pain over varied time periods and to indicate regions of pain. The form was developed by the Pain Research Group of WHO Collaborating Centre for Symptom Evaluation in Cancer Care. Also included are the influence of pain on activities of daily life, quality of life and current medications.

ii. Oswestry Disability Questionnaire: Used to quantify information about how the patient's pain affects their ability to manage everyday life.

iii. Neuropathic Pain Questionnaire: This validated scale rates the presence or absence of neuropathic pain.

iv. PROMIS - Depression: The PROMIS Depression instruments assess self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose).

v. PROMIS - Anxiety: The PROMIS Anxiety instruments measure self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness)

vi. Clinical History and Treatment History: The referring physician will fill out a form containing clinical history, pertinent radiological and electrodiagnostic data and relevant clinical findings. Special attention will be paid to details of the treatment history, the time since onset of painful symptoms and medication history, including present medications.

vii. The EEG technician will obtain a pain rating at the start and end of each EEG session using the 10-point Visual Analog Scale (VAS).

Data Entry Methods

PainQx will provide the clinical site with a tablet and access to an electronic case report form (ECRF) from Survey Analytics to facilitate easy input and analysis of clinical subject information. The ECRF will collect all the subject survey information, clinical, demographic, medication and symptom data.

Quality Assurance

To ensure the validity and integrity of the data PainQx will be conducting monthly data reviews. PainQx will focus on the quality of the EEG collected to ensure that features that accurately reflect

the neurological state of the patient can be readily extracted. PainQx personnel will also monitor the information collected via the ECRF to ensure that patient clinical information is being collected appropriately. Should any problems be identified, PainQx will communicate with the clinical site to address the issue.

Regulatory Issues

Reporting of Severe Adverse Event (SAE) and Adverse Event (AE)

An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study even if the event is not considered to be related to the equipment used for the study. Medical conditions/diseases present before starting the study are only considered adverse events if they worsen after starting the study.

A serious adverse event (SAE) is defined as an event that:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires in-subject hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study test product
    - treatment on an emergency out-subject basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

In the event of any SAE, AE and medical or health emergency, participants will be instructed to call 911 or other emergent care assistance and subsequently report the incident to the PainQx the principal investigator **(William Koppes 240.778.3368)**, PainQx will not be able to assist the participants with any medical emergencies that may occur during the study.

Reporting of IRB actions to NIDA

PainQx will report any IRB actions to Kristopher Bough, Program Manager at NIDA (boughk@nida.nih.gov)

Report of changes or amendments to the protocol

PainQx will report any changes or amendments to the protocol to Kristopher Bough, Program Manager at NIDA (boughk@nida.nih.gov)

Trial Stopping Rules

Study subjects may decide to withdraw from the research study without any penalty and for any reason. Study subjects may be considered withdrawn if they state an intention to withdraw or fail to participate. Although subjects are not required to provide a reason for withdrawal, they will be asked by the research staff about their decision. PainQx researchers also reserve the right to remove a study participant from the study at any time for any reason (e.g., non-compliance with study requirements, safety reasons).

Study subjects may also withdraw permission for the use and disclosure of any of their protected information for research but must do so in writing to the Principal Investigator at the address provided on the first page.

Disclosure of any Conflict of Interest in the DSM

PainQx does not have an existing conflict of interest in the DSM or the clinical trial.

Trial Safety

Risks

Although there is minimal risk in acquiring EEG from a subject, and EEG systems are standard, widely-used medical devices, there is a risk that the technology as deployed for support of the study will not function as anticipated. It will be explained to the participants that these technologies are still evolving and they may experience glitches or malfunctions during the study. There is a chance that patients may experience some slight discomfort during preparation for the EEG procedure (e.g., technician putting on the EEG cap, etc.). Patients may also feel uncomfortable wearing the EEG cap, ear clips, or ECG electrode below the right collarbone. However, patients will be reminded that they are only required to wear the equipment during preparation and for 15 minutes while physiological data is being collected. Additionally, participants may find some questions related to their chronic pain treatment/management to be sensitive. However, participants will be reminded that they do not need to answer any questions that they do not feel comfortable answering.

Benefits

There is clinical-site determined stipend to participate in this study and participants may also

indirectly benefit from the long-term results of this research, which may advance knowledge in the field of chronic pain measurement to help in the diagnosis and treatment of chronic pain.

Trial Efficacy

PainQx will be conducting interim analysis of the data as it is collected to optimize the performance of its algorithms.

DSM Plan Administration

The PI (William Koppes) and the PainQx Clinical Site Manager will track and ensure that the clinical protocol is adhered to and report any adverse events to the National Institute on Drug Abuse (NIDA) via (boughk@nida.nih.gov).

Subjects will be monitored by study staff at the clinical site for the entirety of the 90-minute single visit with no plans for follow-up. Subjects will be provided with study staff contact information during the informed consent process should they want or need to follow up after the testing is completed.

Frequency of DSM

Data will be reviewed monthly during the course of the trial

Protection of Confidentiality

The clinical sites will collect and provide the anonymized patient collected data to PainQx under conditions of strict confidentiality. A unique coded identifier will be assigned at intake to each patient by the site coordinator, and only this code is used as the subject identifier throughout the study. All data will be kept in password-protected files or locked file cabinets. Attention will be rigorously paid to patient confidentiality at all levels of data handling by all study staff. Data will be made available exclusively on a need-to-know basis. Data monitoring will be done quarterly by the Data Monitoring Committee throughout the grant period led by the PI (William Koppes).

PainQx will also not be collecting information on any vulnerable populations such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable.