Title: Efficacy of the Quell Wearable Device for Fibromyalgia

NCT# 03714425

Date: 09/27/2018

RESEARCH DESIGN AND METHODS

We will recruit 100 patients (see the power analysis) with a primary complaint of FM and randomize each of the subjects to one of two treatment conditions: 1) the regular Quell device, and 2) a Minimal Frequency Quell device (control). All participants will be adults age 21 or older and diagnosed with FM. Patients will be invited to participate if they own a smartphone (iPhone or Android device) and can download the pain app and the Quell Relief program app onto their device. Patients will also be included if they (1) have chronic pain related to FM for > 3 months' duration, (2) average 4 or greater on a pain intensity scale of 0 to 10, and (3) are able to speak and understand English. A subject will need to meet the criteria set out by Wolfe et al., for fibromyalgia to be considered for inclusion in this trial: (1) wide spread pain, (2) pain for 3 months or longer, and (3) pain that is not accounted for by any other medical condition (see Table 2). We will also require that the participants have a "physician diagnosis" of fibromyalgia, meaning that they have been told that they have fibromyalgia and the diagnosis was entered in a medical record somewhere.

Patients will be excluded from participation if they meet any of the following criteria: (1) diagnosis of cancer or any other malignant disease, (2) acute osteomyelitis or acute bone disease, (3) present or past DSM-V diagnosis of schizophrenia, delusional disorder, psychotic disorder, or dissociative disorder that would be judged to interfere with study participation, (4) pregnancy, (5) any clinically unstable systemic illness judged to interfere with treatment, (6) a pain condition requiring urgent surgery, (7) an active substance use disorder, such as cocaine or IV heroin use (positive on the Mini International Neuropsychiatric Interview; M.I.N.I. v.5.0), that would interfere with study participation, and (8) have an implanted cardiac pacemaker, defibrillator, or other implanted device. All subjects will be asked to not change their treatment during the study period.

Patients will be equally randomized to one of two experimental groups (High Frequency Quell, N=50, and Minimal Frequency Quell, N=50). The Minimal Frequency Quell will look exactly like the High Frequency Quell but will be programmed to give 2 minutes of stimulation twice during a 1-hour therapy session (2 minutes of stimulation at 0 and 30 minutes, etc.). All subjects will complete assessment measures and be followed for 3 months. Recruitment will not be restricted based on race or ethnicity. Efforts will be made to recruit at least 15% minorities. Since fibromyalgia is identified more often among women than men, we anticipate recruiting 10-15% males. All participants will get assistance in downloading the pain app and have access to a research assistant (RA) who could answer any questions and help manage any problems that the individual may encounter. All participants will also be given a battery of QST testing at baseline and again at the end of the study. We will use an enriched design by first having the potential subjects try the Quell device. We anticipate that less than 5% will decide not to participate in a trial because they dislike the feeling of the Quell. If they find that they would like to use this device they will be included in the study. If they dislike using the device on an initial trial, their age, gender, ethnicity and pain duration will be noted, and the participants will be thanked for their interest in the study and dismissed.

All subjects (High Frequency Quell and Minimal Frequency Quell condition) will be encouraged to use their device for at least 2 therapy sessions (2 hours of stimulation) every day, and to wear the device as often as possible. Tracking of use of the device will be available electronically through the NeuroMetrix Quell app. All demographic and daily pain assessment data will be stored on a secure server (Veracode tested) at BWH and messages will be sent via the 2-way messaging pain app program to help track use of the device. Patients who wish to discontinue the study will be allowed to do so at their request. If the participant is willing, we will meet with her or him to understand reasons for discontinuing the study and problem-solve to see if there is a way to keep following the individual. All subjects will be asked to complete a packet of mailed mid-point assessments approximately 6 weeks after the start of the study and return the completed assessments in pre-addressed stamped envelopes. All subjects will also be asked to complete post-intervention mailed assessments after 3 months. Each subject will be compensated $25 at baseline and $50 at study completion upon receipt of their completed questionnaires. All subjects will be allowed to keep their Quell device at the end of the study. Those subjects assigned to the Minimal Frequency Quell condition will be offered to switch to a High Frequency Quell at the end of the 3-month trial period. It is expected that 15% of the subjects will dropout before completing the study and recruitment of 115 subjects will be needed.

Quantitative Sensory Testing (QST): Mechanical pain: Responses to punctate mechanical stimuli will be measured using a standard set of weighted probes that provide estimates of pain threshold and mechanical temporal summation. Series of 10 stimuli (with 1-second inter-stimulus intervals) will be used to assess the temporal summation of pain that occurs with rapid administration of identical stimuli. A Somedic pressure algometer will be utilized to assess responses to pressure stimulation at several anatomical sites. Pain pressure thresholds (PPT) will be determined twice at each of the following sites on the right and left sides of the body: the trapezius, and thumb. Mechanical pressure will be applied using a 0.5-cm^2 probe covered with 1mm polypropylene pressure-transducing material; pressure is increased at a steady rate of 30 kPA/s until the subject indicates that the pressure has become painful. Finally, we will use cuff algometry to assess responses to sustained mechanical pressure. A Hokanson rapid cuff inflator will be used to inflate a standard blood pressure cuff around the gastrocnemius muscle to a moderately painful level for up to 2 minutes. Participants will indicate when the pressure first becomes painful (i.e., pain threshold) and will provide pain ratings every 30 seconds. As with each of these psychophysical testing procedures, participants are informed that they may terminate the procedure at any time.

Cold Pain Assessment: Responses to noxious cold will be evaluated using a repeated cold pressor task (CPT), which involves immersion of the right hand in a circulating water bath (Neslab RTE17) maintained at a temperature of 4°C. The CPT is the most commonly-used method of pain induction in the laboratory and has demonstrated clinical relevance. Participants will undergo a series of several cold pressor tasks, with the first 2 consisting of serial immersions of the right hand for 30 sec, with 2 min between immersions. Conditioned Pain Modulation (CPM, which refers to the phenomenon of one noxious stimulus inhibiting the pain of a second noxious stimulus) is measured during these cold pressor trials by assessing PPTh during the immersion. The final CPT involves an immersion of the right hand lasting until a participant reaches pain tolerance (or a 3 min maximum). Participants will rate the intensity of the cold pain on a 0-100 scale (“no pain” to “most intense pain imaginable”).

Blinding: The Minimal Frequency Quell is identical to the High Frequency Quell in all aspects with one exception. While the Quell typically delivers 1 hour of continuous stimulation during a therapy session, the Minimal Frequency Quell device will deliver only two 2-minute periods of stimulation every sixty minutes within each therapeutic session. This limited stimulation should

have minimal analgesic effect but should suggest to the subject that they are receiving therapy. Neither the principal investigator, the co-investigators, the research assistant (RA, who will serve as the study coordinator), nor the subject will know if they are given a Minimal Frequency or High Frequency Quell device. The devices will be randomly numbered and provided by NeuroMetrix. At the end of the study, subjects will be asked if they thought they had the Minimal Frequency or High Frequency Quell device. The principal investigator, co-investigators and the RAs will be asked to identify which subjects they thought had High Frequency Quell vs Minimal Frequency Quell, prior to analysis of the data. Both the High Frequency and Minimal Frequency Quell will communicate via Bluetooth with the same mobile application. This application provides the subjects with a dashboard of device information, trending data on device usage, and sleep quality. This same information will be synced to a cloud so that investigators involved in the study can collect this data remotely, as well as monitor adherence with the device. In a past unpublished investigation when this blinding procedure was used among 17 subjects and 11 physicians, Investigators accurately guessed the device (minimal frequency or high frequency) a subject was randomized to in 11 of 17 participants (64.7%). Eleven of 17 (64.7%) study participants accurately guessed the device to which they were randomized. However, there was some discordance between the subjects and the investigators as to who had the minimal frequency versus high frequency devices.

Patient Measures: We will be tracking the patients using validated measures of pain (The Brief Pain Inventory - BPI), fibromyalgia (Revised Fibromyalgia Impact Questionnaire – FIQR), coping (Pain Catastrophizing Scale - PCS), level of disability (Pain Disability Index - PDI), mood (Hospital Anxiety and Depression Scale - HADS), presence of neuropathy (Pain Detect Neuropathic Pain Questionnaire – painDETECT), impression of change (Patients' Global Impression of Change – PGIC), healthcare utilization (monthly clinic and ED visits), and overall satisfaction (Satisfaction and qualitative questions developed for this study specifically related to use of a pain management device; see Table 1). We will also track daily ratings of pain, sleep, activity interference, and mood through the pain app. Objective measures of activity, gait, and sleep will be collected by the devices.

Research Objectives: This study is expected to take 18 months to complete and is designed to gather information about the use of the Quell for persons with chronic fibromyalgia-related pain. We hypothesize that those assigned to using the High Frequency Quell device will report reduced pain compared with those in the Minimal Frequency Quell condition; with those using the High Frequency device also showing improvement in sleep, mood, and level of activity. We hypothesize that frequency of using the Quell (increased tolerability and adherence) will be correlated with greater reduction in pain. We hypothesize that the device will be safe to use and will demonstrate a reduction in healthcare utilization (reduced clinic and ED visits). We will also investigate use of prescription opioids and other nonopioid pain medications among the study subjects and determine the effect of daily use of the High Frequency Quell (vs. Minimal Frequency Quell) on intake of prescription pain medication. Finally, based on preliminary analyses limited by few subject numbers, we will investigate whether certain individuals report greater benefit from using the Quell than others and, in particular, we predict that those with more sensitivity and longer duration of pain will demonstrate most benefit. We will target the PGIC as the primary outcome measure, since it gives a global impression of change in pain, activity limitation, emotions, and overall quality of life. We will target the BPI, FIQR, PCS, PDI, HADS, healthcare utilization, and satisfaction questions as secondary outcome measures.

Power Analyses: Power calculations, as outlined by Cohen (1988), were performed to determine the probability of detecting clinically significant differences between treatment groups in the primary area of measurement: Patients' Global Impression of Change – (PGIC). These calculations assumed a two-tailed test and alpha level of 0.05 confirming the hypotheses that

the Quell would be associated with general overall improvement (e.g., more pain relief, less emotional distress, and less activity interference). In our previous work (Jamison, Wan et al, submitted), we had a high rate of consent to participate among recruited patients, without any significant attrition. We assessed power using a range of plausible parameter values, based on our preliminary data and previously published studies. The power analyses revealed that a sample size of 100 subjects (50 per treatment group), even with 10% dropout, gives the study a >85% probability of detecting a 10-point group difference on a 0-100 rating scale (assuming a standard deviation of 16). Conventional metrics suggest that a 30% change, or difference score, is clinically meaningful, and this sample size would provide adequate power to detect a group difference of approximately 20%. Most of the analyses in the proposed study will involve delta scores reflecting changes within subjects, though the primary analysis of PGIC will compare raw scores rather than change scores (as the PGIC variable is a patient-reported rating of change). Scores of variables used in the secondary analyses should exhibit lower standard deviations than those assumed in the power calculations. We will examine the distribution of the delta scores between groups and will ascertain whether that distribution is normal. This information will allow us to determine whether parametric or nonparametric analyses should be used. Collectively, this sample size (n=100 total), together with our previously-observed very high retention rates and the substantial efficacy of the device, will provide more than adequate power to detect moderate-size effects.