Title: Efficacy of the Quell Wearable Device for Chronic Low Back Pain

NCT# 02944513

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STUDY PROTOCOL - METHODS

This trial is registered at ClinicalTrials.gov (NCT02944513). The Human Subjects Committee of Brigham and Women's Hospital (BWH) will approve the study procedures and written informed consent will be obtained from every participant. Flyers will be distributed about this trial and subjects will be recruited consecutively as they respond to the flyers. We will recruit patients with a primary complaint of chronic low back pain and randomize each of the subjects to one of two treatment conditions: 1) the hfTENS device or 2) treatment-as-usual control (no device) using a random number table (https://www.graphpad.com/quickcalcs/randomize1.cfm). All participants will be adults age 21 or older and diagnosed with axial musculoskeletal or discogenic back pain with or without radiculopathy. There will be a number of other inclusion criteria: (1) participants will need to own a compatible smartphone, either Android or iPhone, (2) they will have to have evidence of chronic pain for over 6 months and average ≥4 on a 0-10 pain intensity scale, and (3) they will need to understand and speak English. Study exclusion criteria will include (1) diagnosis of cancer, (2) evidence of osteomyelitis, (3) a psychiatric disorder judged to interfere with the study (e.g., psychosis or delusional disorder), (4) an active substance abuse disorder (e.g., cocaine or heroin use), (5) surgery scheduled within 3 months, (6) pregnancy, (7) an implanted device (e.g., pacemaker), and (8) any unstable systemic illness judged to interfere with treatment.

During the 3-month study period all participants will be discouraged from making changes in their pain management regimen.

We will employ the use of a smartphone pain app in this study,[16,17] which was designed to collect daily assessment data as well as demographic and medical information. It was devised to help monitor daily patient progress over the period of the trial. All subjects will be informed how to find the apps ('Quell Relief' and 'BWH Painapp' either on the App Store or Google Play) and will be assisted in downloading the apps, if assistance is needed. The pain app has built-in daily reminders for the user with push notification to complete daily assessments as well as 2-way messaging to connect with study staff.

Patients will be randomized to either the Experimental group with use of a hfTENS or Control group with treatment as usual. Both groups will be asked to use the smartphone pain app to monitor their daily assessments. All subjects will complete a packet of validated questionnaires and will be followed for 3 months. All participants will sign an informed consent form and will be given assistance in downloading the apps by a research assistant (RA) who will answer any questions and help to manage any problems that the individuals might encounter. All participants will be also administered QST at baseline.[11,12]

Patients randomized to the experimental group (hfTENS) will be encouraged to use the device at least two hours every day. Tracking of use of the device will be available electronically through the hfTENS app. All demographic and daily pain assessment data will be stored on a secure server (Veracode tested) and messages will be sent via the 2-way messaging pain app program to help track use of the device and

to address any problems that the subjects might encounter. All subjects will be also asked to complete post-intervention mailed assessments after 3 months and return the completed assessments in pre-addressed stamped envelopes. Each subject will be compensated $25 at baseline and $50 at study completion upon receipt of their completed assessments. All subjects will be allowed to keep their hfTENS device at the end of the study. Those subjects assigned to the Control condition will be offered a hfTENS device at the end of the 3-month trial period.

Brief Quantitative Sensory Testing

Pressure pain thresholds (PPThs) will be assessed using a standard manual pressure algometer *(Wagner Force Ten Digital Force Gage; www.wagnerinstruments.com)*. PPThs will be evaluated at the trapezius muscles bilaterally and at the wrists bilaterally (four sites) by a trained and experienced RA. A 0.5 cm^2 probe covered with a rubberized pressure-transducing material will be applied twice to each site to measure PPThs. Mechanical force will be gradually increased until the subject verbally indicates to the tester that the pressure is “painful.” Temporal summation of mechanical pain will be assessed using weighted pinprick stimulators at each of the metacarpophalangeal joints of the middle fingers with a *Touch-Test Sensory Evaluator (www.ncmedical.com*).[14] The subjects will be instructed to indicate which of the probes produced a painful sensation (usually the 128 or 256 mN gauge) and this stimulator will be used to apply a series of 10 sequential stimuli at the rate of 1 per second to the dorsum of the hand. The RA will ask the subjects to indicate their perceived level of painfulness of the first, fifth, and tenth stimulus. The degree of mechanical temporal summation will be determined by the increase in pain (as rated by the subject) between

the first and last stimulus. We and other groups have frequently employed these QST procedures in prior studies among patients with a broad array of musculoskeletal chronic pain conditions.[11,12,18]

Patient Measures

Participants will complete measures recommended by the Initiative on Methods, Measures, and Pain Assessment in Clinical Trials (IMMPACT)[19] as primary outcomes. All participants will be asked to complete a series of baseline questionnaires. Identical questionnaires will be mailed to the subjects for completion after 6 weeks and again after 3 months. All subjects will be supplied with self-addressed stamped envelopes to mail back their completed questionnaires. The following measures will be administered to the study patients: (1) The Brief Pain Inventory (BPI).[20,21] It has been shown to have excellent reliability and validity among samples of chronic pain patients; (2) The Pain Disability Inventory (PDI).[22] This is a 7-item questionnaire designed to assess activity-related disability in performing household chores, recreational and social activities, work-related and sexual activities, general activities of daily living, and life-supporting behavior. It has been shown to have excellent reliability and validity; (3) The Pain Catastrophizing Scale (PCS).[23,24] This is an instrument that examines the propensity for recurring intrusive ruminating thoughts. Persons scoring high on this scale tend to magnify and amplify their pain and show signs of helplessness. It has good psychometric properties with adequate reliability and validity; (4) The Hospital Anxiety and Depression Scale (HADS).[25,26] This is a valid and reliable measure of anxious and depressive symptoms over the past week. The HADS has been used extensively in

clinics to assess mood and has been shown to have an optimal balance between sensitivity and specificity.

Once a week the subjects will be called by the RA and asked to rate their current progress on a 0=no pain/no interference to 10=worse possible pain/extreme interference on the following items: 1) current pain intensity, 2) average pain intensity, 3) pain interference on activities of daily living, social activities, outdoor and recreational activities, sleep, appetite, work ability, and 4) anxiety, depression and irritability from 0=stable mood to 10=worse possible mood. All questions were developed and standardized from a previous study.[27] All subjects will be asked about their current pain medications and all changes in prescription pain medications will be noted. Participants assigned to the Experimental group will be also asked which leg they used the hfTENS on over the past week and all subjects will be given the opportunity to share any additional thoughts about the study.

At 3-month post-treatment all patients will be sent a packet of the baseline questionnaires to complete again and return by self-addressed stamped envelopes. Those in the Experimental group will be also asked to respond to a 14-item helpfulness questionnaire designed to investigate the perceived benefit of the hfTENS. Those in the Control group will complete helpfulness questions only about the study and perceived helpfulness of the pain app. All items, which were developed in a prior study,[18] and adapted from a previously validated measure,[28] will be rated on a 0 to 10 scale (e.g., not at all helpful to very helpful) and assessed helpfulness, bothersomeness, ease of use, how often they used the device, and whether the user was willing to use the hfTENS in the future.

Statistical Analysis Plan

The aim of this study is to establish the safety, efficacy, feasibility, and tolerability of the hfTENS device for use among chronic back pain patients. We will use an intent-to-treat analysis and all variables will be assessed using univariate and multivariate analyses to establish group differences at baseline and follow-up. Although this will be designed as a preliminary study, power calculations, as outlined by Cohen,[29] will be performed to determine the probability of detecting clinically significant differences between treatment groups in the primary area of measurement: pain intensity. These calculations will assume a two-tailed test and alpha level of 0.025 confirming the hypotheses that the Quell would be associated with general overall improvement (e.g., more pain relief). A more rigorous $p<0.025$ significance level will be established rather than $p<0.05$ because of the multiple observations. The power analyses is expected to reveal that a sample size of 60 subjects (30 per treatment group), gives the study a >80% probability of detecting a 1.5-point group difference on a 0-10 rating scale. Depending on the nature of the variables, chi-square, t-tests, and logistic regression analyses will be conducted. We also will examine and report on the qualitative responses of the participants in using the hfTENS. Group differences will be assessed using repeated measures ANOVA and preliminary mixed linear regression model analyses, as appropriate.