
Quell Opioid Reduction and Pain Relief in Patients with Cancer

STUDY PROTOCOL

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TABLE OF CONTENTS

Table of Contents	3
Abbreviations and Definitions	4
1. Rationale and Purpose	6
2. Study Background	6
3. Study Design	8
4. Criteria for Evaluation	9
5. Subject Selection	10
-Inclusion	
-Exclusion	
6. Concurrent Medications	10
7. Study Procedures	11
8. Evaluation By Visit	12
9. Data Storage	14
10. Statistical Analysis	14
11. Discontinuation and Replacement of Subjects	15
12. Potential Risks	16
13. Potential Benefits	16
14. Risks/Benefits Ratio	17
15. Alternative Treatments	17
16. Payment and Costs	17
17. Informed Consent	17
18. Confidentiality of Data and Privacy of the Individual	17
19. Safety	18
20. Monitoring	18
21. Record Retention	19
22. Publication	19
23. Facilities and Personnel	19
-Site Selection	
-Clinical Trial Agreement	
-Personnel Training	
-Center Readiness	
24. References	21
25. Appendix	24

Abbreviations and Definitions

ADVERSE EVENT	Any untoward medical occurrence in a patient or clinical investigation. This study will report events related to data collection or loss of privacy.
CRF	Case report form
CURES	Controlled Substance Utilization Review and Evaluation System
DSMB	Data Safety Monitoring Board
EORTC Cancer	European Organization for Research and Treatment of Cancer
HIPAA GUIDELINES-	Health Information Portability and Accountability Act Practice
IRB	Institutional Review Board
MOS	Medical Outcomes Study
PGIC	Patient Global Impression of Change
SERIOUS ADVERSE EVENT	Events that result in death, are life threatening, requires or Any medical event that is considered serious and may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the serious definition.
SF-MPQ	The short form McGill Pain Questionnaire
STSI	Scripps Translational Science Institute
TENS	Transcutaneous Electrical Nerve Stimulator
WINS	Wearable Intensive Nerve Stimulation

1. Rationale and Purpose

Study Abstract: Quell is a class II medical device with FDA 510(k) clearance for the symptomatic relief and management of chronic intractable pain, without a prescription. It operates by using an electrical stimulator to activate peripheral sensory nerves and trigger analgesia. This device has great potential for significantly decreasing opioid use in patients

who have chronic pain secondary to serious illnesses and thus improve their quality of life, but has not yet been tested for cancer related pain. This study investigates the utility of the device in improving pain in patients with cancer while decreasing their overall opioid consumption.

Hypothesis: We hypothesize that Quell and its associated mobile application will decrease the overall opioid consumption of our test population while providing pain relief as self-reported by the study participants.

Purpose of the Study Protocol: To study effects Quell has on opioid consumption and pain relief in patients with cancer.

Rational: The prevalence of pain is high in patients with advanced chronic illness such as cancer. Despite increasing interest in, and efforts to improve its management, pain remains poorly controlled in nearly half of all patients with cancer, with little change in the past 20 years. (1). The prevalence of cancer-related pain has ranged from 14% to 100% depending on what surveys are evaluated, (2) and the incidence of pain has been shown to be similar across stages of disease. (3). Further, it has been shown that previously healthy people can be severely debilitated with poor quality of life during or even after curative treatments leave them with continued pain (4,5). Opioids are the mainstay of the medical management of moderate to severe pain and are used, in addition to appropriate adjuvants, by oncologists and palliative medicine physicians to help manage cancer related pain. However, given the associated side effects and the stigma of opioids both on the part of the patients and some providers, these medications do not always adequately relieve the patient's pain. Neuropathic pain in particular, is a challenge because while opioids and their adjuvants do help, there is no clear consistent medication that is proven effective above the rest (6).

Quell is a novel Wearable Intensive Nerve Stimulation (WINS) device that has FDA clearance for treatment of chronic pain continuously, including during sleep. Its mechanism of action is based on Transcutaneous Electrical Nerve Stimulation (TENS). It utilizes a precise high power electrical stimulator to activate peripheral sensory nerves and trigger analgesia. Though this device has efficacy for chronic and neuropathic pain (7), it has yet to be tested in this highly needed patient population, and has immense potential to significantly improve their quality of life.

2. Study Background

In 2015, 14.5 million Americans were living with a recent or remote history of cancer. (8,9). Pain is among the most, if not the most distressing sequelae of cancer and its associated treatments, and remains poorly managed worldwide. The devastation of living with uncontrolled pain has a significant effect on quality of life, physical functioning, and psychological distress.

Cancer related pain develops from complex interactions among cancer cells, the immune system, and the peripheral and central nervous systems (10,11). Cancer cells and the local immune cells produce a wide range of substances that stimulate the pain receptors. Once pain receptors are stimulated, impulses are transmitted first by afferent A δ fibers and then by separate slower C fibers. These fibers end in cell bodies in the dorsal root or trigeminal ganglion, which then interact with neurons in the central nervous system cells in the spinal cord. These cells synapse to the contralateral thalamus from which impulses are transmitted to regions of the cortex via somatosensory pathways. Visceral pain arising from nociceptors in internal organs is mostly transmitted by C fibers. It is often less well localized and less sharp than somatic pain, and is triggered by direct irritation from the tumor, distention.

The subjective nature of cancer pain derives in part from the perception of pain. The perception of pain is known to vary depending on factors such as anxiety, depression, distraction, etc. These factors have no direct relationship to the pain receptors, or the painful stimulus caused by the interplay between the cancer cells and immune cells. However, the fact that these factors impact the pain overall, indicates the presence of additional mechanisms that alter pain transduction and perception (12). One mechanism is the descending inhibition from midbrain and higher regions that contain high concentration of opioid receptors. Various neurotransmitters are involved in mediating this pain inhibition pathway including GABA and serotonin, but most important are the endogenous opioids, explaining why synthetic opioids work so well to inhibit pain (13).

The pain gate theory states that activation of sensory nerves (A β fibers) closes a “pain gate” in the spinal cord that inhibits the transmission of pain signals carried by nociceptive afferents (C and A δ fibers) to the brain (14). Although it is activated by localized peripheral nerve stimulation, the descending pain inhibition system has analgesic effects that may extend beyond the stimulation site to provide broad pain relief (15-19).

High frequency nerve stimulation, such as with a WINS device, induces an elevation in enkephalins that act through the δ -opioid receptor (20,21). Synthetic opioids mostly act through μ and κ -opioid receptors. All three of these receptors are involved in descending pain inhibition.

Clinical researchers have reported good clinical success with cutaneous electrical stimulation using 16 different electrical currents, assembled into packages, and transmitted to the existing nerves using modified electrocardiogram pads for 30 minutes a day (22,23).

TENS is characterized by a number of electrical parameters including the stimulation pulse shape, amplitude, duration, pattern, and frequency (24). Although all the parameters can be adjusted in an attempt to achieve maximal analgesia, only pulse intensity (24,25-27) has a clear influence. Stimulation at an intensity below the level of sensory perception does not provide pain relief, and the degree of analgesia is correlated to the stimulation intensity (28).

Quell is a wearable, automated electrical nerve stimulator designed for people with pain, that includes technology to provide convenience while optimizing pain relief. It consists of four components: a therapy pod, an electrode array, a band, and a mobile app. The therapy

pod, which contains the electronics, is placed in the band and then an electrode array is attached by snapping it to the therapy pod. The electrode array consists of 4 hydrogel pads that provide a large (60 cm²) interface between the stimulator and the patient's sensory nerves. The hydrogel typically lasts 2 weeks or 100 hours of use, and is formulated to reduce skin irritation. The band is placed on the upper calf where therapy is initiated by pressing the button. The reason for placement on the upper calf is that this area has a high density of cutaneous sensory innervation that enables robust stimulation of A β fibers. When placed on the upper calf, the electrode array is circumferential and will stimulate sensory dermatomes S2- L4 providing a broad neural input to trigger analgesia through the descending pain inhibition system.

A calibration procedure is used to estimate the optimal therapeutic stimulation intensity (within the recommended range) for each patient. This is accomplished by an algorithm that automatically determines an intensity within the recommended therapeutic range that is appropriate for the patient. Once calibrated, all subsequent therapy is automatically delivered at the required intensity. The patient has the option of manually adjusting intensity at any time and the device incorporates these changes in subsequent therapy sessions. Quell automatically compensates for nerve desensitization by adaptively increasing the intensity over the course of the one-hour therapy session. The device enables long- term unattended therapy, such as overnight, by automatically restarting hour-long therapy sessions every other hour as long as the device remains on the leg. It also monitors the amount of time it is on the same region of skin and alerts the patient to ventilate the area to reduce the risk of irritation. Finally, Quell has embedded intelligence to determine if the patient is sleeping and automatically reduces the intensity to provide overnight pain relief without disturbing sleep.

The therapy pod is powered by a Lithium-Ion battery that provides 30-40 hours of therapy (4-7 days of typical use) if fully charged. The battery can be recharged in 2-3 hours by plugging the device into an AC adapter.

3. Study Design

The study is a single site, double blinded, placebo controlled randomized clinical trial. 40 subjects will be selected based on the inclusion criteria stated below and then randomized to either the intervention group or the placebo control group. Prior to the start of this study, a Controlled Substance Utilization Review and Evaluation (CURES) reports will be acquired to establish baseline number of opioid prescriptions for each subject. Subjects will track how consistently they are using pain medications, both opioids and non-opioids, during the two weeks prior to the start of the study. They will also provide twice daily recordings of their pain intensity via a mobile application. At the end of this two-week period, each subject will be fitted with a Quell or a sham device, including initial calibration to the subject's comfort level as described in the background section.

The sham device is identical to Quell in all aspects with one exception. While Quell delivers 1 hour of continuous stimulation during a therapy session, the sham device delivers three 2-minute periods of stimulation at 0, 28 and 58 minutes within the therapeutic session. This limited stimulation should have little to no analgesic effect but should suggest to the subject that they are receiving therapy.

Neither the principal investigator, nor the co-investigator or the subject will know if they are given a sham device or the actual Quell device. The study coordinators will be the only ones who will be aware of which intervention subjects receive. At the end of the study, subjects will be asked if they thought they had the sham or actual device. Both the principal and the co-investigator will be asked to identify which subjects they thought had Quell vs the sham device, prior to analysis of the data.

Once the study subjects have started using the device, we will also be able to monitor and track their sleep wirelessly via the mobile application as long as they are wearing the device. Subjects will receive weekly check in's to monitor the functionality of the device and to help troubleshoot any issues with the device for the duration of subject participation in the study. These check-ins will take place in person, by phone, and or per subject's usual outpatient oncology visits. Each subject will use their device for 8 weeks, during which they will continue to track their pain, sleep and frequency of pain medication use as stated above. Study investigators will receive automated alerts via email to ensure that study are participants using their devices and that the devices are powered on at regular intervals for the duration of the study.

Both Quell and the sham device 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.

Total duration of subject participation will be 10 weeks.

4. Criteria for Evaluation

Primary Efficacy Endpoint

The primary endpoint is a reduction in daily opioid use assessed at weeks 2, 4, 6, 8 and 10 of the study as recorded by the subject in their analgesia diary. This diary will be a preformatted paper form given to each subject at the start of the study, and will include the name and dosage of all the analgesic pain medications prescribed to the subject, as well as any over the counter pain medications the subject will be using. The subjects will be asked to log what times they take their pain medication each day. This diary will then be reviewed and logged into our secure database at each of the clinic visits as stated above. Per previous studies with a similar design, a 20-30% change in opioid consumption is clinically relevant. This end point is chosen as the overall goal of this study is to provide a novel way for patients with cancer to have optimal pain control while reducing their overall opioid use.

Secondary Endpoints

Change in pain intensity via the mobile app and as described by the subject using the Short-form McGill Pain Questionnaire-2 SF-MPQ-2 and the Patient Global Impression of Change (PGIC). The pain intensity scores will be measured twice daily using the mobile application and the SF-MPQ-2 will be completed during weeks 0,2,4,6 and 10 of the study. The PGIC will come completed at week 10.

These tools were chosen because a treatment should demonstrate a statistically and a clinically significant effect. Well-researched cutoff method suggests, that a 30% reduction of pain can be considered clinically significant (29). This level corresponds with a 2 points on a 0 to 10 pain intensity numerical rating scale (30). The Short-form McGill Pain Questionnaire (SF-MPQ-2) assesses the major symptoms of both neuropathic and nociceptive pain and can be used in studies of epidemiology, natural history, pathophysiologic mechanisms, and treatment response. Numerous studies have demonstrated its reliability, validity, and responsiveness in diverse samples of subjects with acute and chronic pain. Subjects rate their pain in sensory and affective terms and use a visual analog scale. The self-report measure Patient Global Impression of Change reflects a subject's belief about the efficacy of treatment. It is well studied and widely used in chronic pain clinical trials. PGIC is a 7-point scale depicting a subject's rating of overall improvement of a treatment intervention. Subjects rate their change as “very much improved,” “much improved,” “minimally improved,” “no change,” “minimally worse,” “much worse,” or “very much worse.”

Changes in quality of life as measured by the Functional Assessment of Cancer The EORTC Quality of Life C-15- PAL measurement scale assessed at time of enrollment (week 0) week 6 and week 10 of the study. This is a validated questionnaire developed to assess the quality of life of palliative care cancer subjects.

Additional analysis includes changes in objective sleep measures using the mobile application and also The Sleep Scale developed for the Medical Outcomes Study. We will also look at the other characteristics of the pain that are automatically monitored with Quell/Sham device and its mobile application such as activity level.

5. Subject Selection

Study Population

40 Subjects with a diagnosis of metastatic cancer of any type, with cancer related pain on active chemotherapy treatment, who meet the inclusion and exclusion criteria will be selected for participation in this study

General Inclusion Criteria:

1. Male or Female greater than or equal to 18 year of age at visit one.
2. Documented diagnosis of metastatic cancer, who has cancer/chemotherapy related pain, with a prognosis of 6 month or greater as determined by the primary oncologist.

3. Visual evidence that subject owns a smart phone and is able to use basic mobile applications such as downloading an app, opening the app, and performing one simple task within the app.
4. Subject speaks and reads English fluently.
5. Subject able to understand and grant informed consent.
6. Live in an area with cellular data connectivity available as provided by the subject.
7. Documented adherence with clinic follow up visits per medical records.
8. Subject using at least one opioid medication on a daily basis.

Exclusion Criteria:

1. Subject has a cardiac pacemaker, implanted defibrillator or other implanted electronic device.
2. Inability to complete subjective data as required; e.g. on mobile application and questionnaires.
3. Does not live in an area with suitable cellular data connectivity.
4. Has infrequent scheduled clinic visits.

Subject Recruitment

Subjects will be recruited from the Scripps Mercy Oncology Clinic, San Diego California.

6. Concurrent Medications

All subjects should be maintained on their same oncology treatment protocol as directed by the primary oncologists during the study as they were prior to the onset of the study. Any changes in medication type, doses and frequency should be discussed with the treating physician and documented.

7. Study Procedures

7.1 Enrollment

Subjects meeting eligibility criteria will be screened by the primary investigator and treating oncologist. Subjects will be introduced to the study during their scheduled oncology and or palliative care visit. Study information will be made available to the subjects. Those interested in the study will be provided with the informed consent, enrolled in the study and provided with the materials necessary for participation in the study.

7.2 Measures of Adherence and Treatment

By using the mobile application, subjects will automatically be keeping a diary that time stamps each entry of pain intensity. Further, the mobile application communicates with Quell and the sham device via Bluetooth and thus also monitors the usage of the device. The questionnaires as stated above will be completed either at the clinic visits as detailed below, or if the subject cannot make it to the clinic visit, the questionnaire will be completed over the phone by the study investigators. The results of these questionnaires will be stored in a HIPAA compliant central data hub.

7.3 Data collection

After informed consent has occurred, all subjects will be asked questions regarding socio-demographics, age, ethnic background, gender, height, weight, medical and related family history (ie. cancer, psychiatric diseases, substance misuse and abuse). Additionally, they

will be educated on how to input their pain intensity into the mobile application; and separately how to record their pain medication use using a paper analgesic diary.

Quality of life assessment will be conducted in person at the enrollment visit (week zero), and again at weeks 6 and 10.

Assessments entered into the mobile application including, pain assessments and sleep monitoring will sync wirelessly through cloud data base and will only be accessed by approved personal directly involved in the study. Anonymized data will be stored in a HIPAA compliant central data hub.

7.3.1 Concomitant Medications

All concomitant medications and concurrent therapies will be documented at screening and each scheduled clinic visit. A CURES report will be retrospectively generated for one month at time of enrollment, then every four weeks for the duration of the study.

7.3.2 Socio-Demographics

Demographic information (date of birth, gender, ethnicity, race) will be recorded at screening

7.3.3 Medical History

Relevant medical history, including history of current disease, pertinent family history, and information regarding underlying diseases will be recorded at Screening.

7.3.4 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed during their regular scheduled visits and recorded as part of this study. If study visits occur outside of scheduled clinic visits, vital signs will not be performed or recorded.

7.3.5 Adverse events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

7.3.6 Study Visits

Investigators will attempt to schedule study visits so that they coincide with subject's oncology visits in order to not add any additional burden. If these dual visits cannot be scheduled and study visit needs to occur in person, subject will receive compensation for time and travel.

8. Evaluations by Visit

8.1 Visit 1 (Week 0)

1. Review the study with the subject and obtain written informed consent and HIPAA authorization.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history, including a history of diagnosis date, and prior treatments.

5. Record concomitant medications.
6. Perform and record vital signs.
7. Download and set up mobile application on subject's phone.
8. Educate subject on how to use mobile application.
9. Have subject demonstrate knowledge of how to use application.
10. Perform and record the SF-MPQ-2, opioid assessment and Quality of life Assessment.
11. Provide them with their analgesic diary and educate them on how to use it
12. Schedule subject for visit 2 weeks.

8.2 Visit 2 (Week 2)

1. Record any Adverse Experiences as needed.
2. Review Mobile Application Pain assessment.
3. Review documentation of analgesic use.
4. Perform and record vital signs.
5. Give subject Quell/Sham device, make sure subject properly calibrates.
6. Educate subject on how to use the device and to adjust intensity if needed and communicate that stimulation should feel "strong but comfortable".
7. Schedule follow up phone calls for subject to help trouble shoot and field questions on the device.
8. Perform and record the SF-MPQ-2.
9. Perform and record the results of the MOS Sleep Scale.
10. Schedule follow up visit for 2 weeks.

8.3 Visit 3 (Week 4)

1. Record any Adverse Experiences/troubleshoot any questions or concerns.
2. Review mobile application for adherence use.
3. Record changes to concomitant medications.
4. Perform and record vital signs.
5. Review Mobile Application Pain and Sleep assessment.
6. Review documentation of analgesic medication use.
7. Perform and record the SF-MPQ-2.
8. Schedule follow up visit for 2 weeks.

8.4 Visit 4 (Week 6)

1. Record any Adverse Experiences/troubleshoot any questions or concerns.
2. Record changes to concomitant medications.
3. Review mobile application for adherence use.
4. Perform and record vital signs.
5. Review Mobile Application Pain and Sleep assessment.
6. Review documentation of analgesic medication use.
7. Perform and record Quality of life Assessment and SF-MPQ-2.
8. Perform and record the results of the MOS Sleep Scale.
9. Schedule check in phone calls as needed.
10. Schedule follow up appointment in 4 weeks.

8.5 Visit 5 (Week 8)

1. Over the phone unless otherwise scheduled to come into clinic.

2. If over the phone only; Review documentation of analgesic use.
3. If scheduled to come in; visit 5 will mirror Visit 3 (Week 4).

8.6 Visit 6 (Week 10)

1. Record any Adverse Experiences/troubleshoot any questions or concerns.
2. Record changes to concomitant medications.
3. Review mobile application for adherence of use.
4. Perform and record vital signs.
5. Review Mobile Application Pain and Sleep assessment.
6. Review documentation of analgesic medication use.
7. Perform and record SF-MPQ-2 and Quality of life Assessment.
8. Collect Quell/Sham device and delete mobile application from subject's phone.
9. Administer the PGIC, the MOS Sleep Scale survey and record the results.
10. Provide subject with results of any preliminary data analysis pertinent to their involvement in the study.
11. Address any remaining question or concerns regarding subject's participation in the study.

8.7 Early Withdrawal Visit

1. Record any Adverse Experiences/troubleshoot any questions or concerns
2. Record changes to concomitant medications.
3. Review mobile application for adherence of use.
4. Perform and record vital signs.
5. Review Mobile Application Pain and Sleep assessment.
6. Review documentation of analgesic medication use.
7. Perform and record SF-MPQ-2 and Quality of life survey
8. Collect Quell/Sham device and delete mobile application from subject's phone
9. Administer the PGIC.
10. Provide subject with results of any preliminary data analysis pertinent to their involvement in the study.
11. Address any remaining question or concerns regarding subject's participation in the study.

9. Data Storage

All data will be transmitted and stored to HIPAA compliant encrypted standards.

Future research:

Subject information will be kept for at least 2 years after completion of this study and up to 20 years for future research that has not yet been planned. Future research using the data will first be approved by Scripps IRB. After 2031, the code that links the sample to the subject's traditionally-identifying information will be destroyed. Related de-identified health information will be kept indefinitely for future research studies at Scripps in secure databases.

10. Statistical Analysis

A biostatistician will perform all data analysis. The sample size (20 participants per group) achieves 80% power to find a 20% (absolute) difference in mean percent change in opioid consumption between the two groups with an estimated standard deviation of mean percent change of 22% and 90% power with an estimated standard deviation of 19% in both groups using a two-sided two-sample t-test with a significance level (alpha) of 0.05.

Descriptive statistics will be calculated for baseline characteristics of both study groups and to assess the effectiveness of the randomization. Repeated measures analysis will be used to assess changes in opioid medication use, pain assessments, and quality of life measures over time in the intervention group compared to the control group. Mid study analysis will be conducted with all data amassed around week 6 of all subjects enrolled.

11. Discontinuation and Replacement of Study Participants

11.1 Early Discontinuation of Quell/Sham Device

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 6) should have an early discontinuation visit. Refer to Section 8 for early termination visit. Subjects who withdraw after Visit 4 but prior to Visit 6 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

11.2 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced, as long some data has been collected from the device. This withdraw will be accounted for in our data analysis. Should subjects withdraw from the study without ever using the device, their device will be collected and they will be replaced with a new participant.

11.3 Protocol Violations

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Include other specific examples as appropriate for the study (non-adherence with study drug regimen, etc.)

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

12. Potential Risks

Risk from the device:

Transcutaneous electrical nerve stimulation therapy is considered mostly safe. On rare occasions, an electrical current will be too intense for a subject, causing irritation on the skin. On very rare cases, some subjects have reported some calf muscle cramping with prolonged use.

Some subjects with skin allergies may react to the electrode pads used with the units. People with pacemakers, infusion pumps, defibrillators, and similar devices should not be exposed to the electrical currents produced by transcutaneous electrical nerve stimulation.

Psychological or Social Risks Associated with Loss of Privacy:

In spite of all the safety measures that we will use, we cannot guarantee that the subject's identity will never become known. Every effort will be made to secure the information stored on the mobile application and the information uploaded into the cloud database. In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on any documentation submitted to the Sponsor.

13. Potential Benefits

Subjects enrolled in this study have the potential to have their pain adequately managed while down titrating their overall opioid use. There may be no direct benefit to the subject

for participating in this study. Knowledge gained by conducting this study may lead to the identification of mechanisms that may lead to improved detection and treatment of subjects with cancer related pain.

14. Risk-Benefit Ratio

There is minimal risk of physical harm with any of the devices used. As with any electronic means of communication, no matter how secure, there is always a risk of a data breach.

15. Alternative Treatment(s)

This study involves the addition of a drug free wearable pain device. Subjects may refuse participation in this study and this will not influence their care in any way.

16. Subject Payment/Costs

Subjects will be paid per study visit. Additionally, should they choose, they can keep the Quell device as well as 6 months worth of electrodes. Subjects who were assigned the sham device will be given the option of using and keeping the Quell device.

17. Informed Consent

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB.

The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB.

The study personnel that have been trained on this study protocol by the sponsor (investigator, designated co-investigator or research coordinator) will obtain informed consent for this study. Subjects will be given ample time to read and understand the consent form in their native language. Subjects will have an opportunity to ask the investigator and or coordinator questions and have all questions answered before signing. Once the subject has signed the informed consent, a copy will be given to them. The original consent will be filed at the study site.

18. Confidentiality of Data/Privacy of Individuals

Scripps Translational Science Institute affirms the subject's right to protection against invasion of privacy. Data files are stored on a password-protected computer/database and will be accessible only to the above listed investigators and research staff. Subject's data

will be assigned and identified by a unique code. Traditional identifying information such as name, address, phone, medical record number, etc will not be included in the database. Only the investigators and the research staff will have the link that can match the code to identifying information. Study files will be kept in secure locations at each study site.

19. Safety

Adverse Events:

Any event that occurs during the study period and is considered to be directly related to the study procedures will be considered an adverse event. All possible events will be reported to Scripps Translational Science Institute. Loss of privacy would also be considered a reportable adverse event.

Serious Adverse Events:

We do not anticipate any serious adverse events related to this study. However, events that fit the definition of a serious adverse event according to ICH guidelines must be reported to STSI within 24 hours.

Such events include any untoward medical occurrence that is life threatening, results in death, requires hospitalization or prolongation of existing hospitalization, and/or results in persistent or significant disability/incapacity. Medical Events that may not be immediately life threatening or result in death or hospitalization should also be considered serious when they jeopardize the subject or require intervention to prevent one of the other outcomes listed in the serious definition.

The study Principal Investigator at Scripps will review adverse events and serious adverse events directly related to loss of privacy. This study does not have a Data Safety Monitoring Board.

20. Monitoring

STSI will monitor the study throughout its duration. The study monitor will visit the site at appropriate intervals to review investigational data for accuracy and completeness and to ensure adherence with the protocol. The investigator/site will permit access to all documents and records maintained on the subjects in the study. Source documents will be reviewed to ensure all subjects have properly signed and dated the informed consent/HIPAA forms. All information will be reviewed to ensure eligibility criteria as per the protocol, and supporting source data will be verified. The Investigator and/or research coordinator must be available for monitoring visits. STSI will collect the appropriate regulatory documentation from each clinical site according to ICH/GCP guidelines. Regulatory document records at the site will also be reviewed periodically during monitoring visits for accuracy and completeness.

*Enrollment may not begin at the study site until all required documentation is collected, key study personnel are trained and written approval from STSI is given to start enrollment.

21. Record Retention

Research records will be kept for at least 2 years after study completion. Scripps will continue to store and use the subject information for up to 20 years. In 2031, the code that links the subject to the identifying health and trait information will be destroyed. The data and related de-identified health and trait information may be kept indefinitely. Record retention must also comply with any specific requirements of the local reviewing IRB. (i.e. Scripps- must keep HIPAA form for at least 6 years after study completion)

Records will ultimately be kept at the research site until STSI has given written permission to destroy the records. If record retention cannot be maintained by the participating sites, STSI must be notified and storage will be provided.

22. Publication

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

23. Facilities and Personnel

Site Selection

Investigators and participating centers will be selected at institutions with access to an established IRB or equivalent that meets on a regular basis. An interest in participating in the study and willingness to support monitoring and auditing procedures will be prerequisites. Other considerations include the center's ability to execute the study protocol and a prospective subject population that will meet the protocol criteria.

Clinical Trial Agreement

A Clinical Trial Agreement must be signed by all parties named in the Clinical Trial Agreement and returned to Scripps Translational Science Institute prior to the commencement of any study activities.

Personnel Training

Center personnel (investigators, coordinators, and other key clinical staff) will be trained by the sponsor on the study protocol and study activities relevant to their role prior to conducting any study activities. Training will also include but is not limited to smartphone device setup and continual use, case report form (CRF) completion, and use of an electronic data capture program.

It is the responsibility of the study site investigator to ensure that there are ample staff to complete the study according to the protocol and the entire research staff designated to this

study has the education and the training required to perform the proposed procedures, and the procedures are allowed under the scope of practice.

Center Readiness

All local regulatory requirements need to be fulfilled and each study center must have written documentation of center/investigator readiness provided by Scripps Translational Science prior to enrolling any subjects in the study.

24. References

1. Smith TJ, Saiki CB. Cancer Pain Management. Mayo Clin Proc. 2015 Oct;90(10):1428-39. doi: 10.1016/j.mayocp.2015.08.009. Review.PMID: 26434968
2. Goudas LC, Bloch R, Gialeli-Goudas M, Lau J, Carr DB. The epidemiology of cancer pain. Cancer Invest. 2005;23(2):182-190.
3. Van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007;18(9):1437-1449.
4. Lewis MA, Zhao F, Jones D, et al. Neuropathic symptoms and their risk factors in medical oncology outpatients with colorectal vs. breast, lung, or prostate cancer: results from a prospective multicenter study. J Pain Symptom Manage. 2015; 49(6):1016-1024.
5. Pachman DR, Barton DL, Swetz KM, Loprinzi CL. Troublesome symptoms in cancer survivors: fatigue, insomnia, neuropathy, and pain. J Clin Oncol. 2012;30(30):3687-3696.
6. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-173.
7. Shai N. Gozani, M.D., Ph.D Science Behind Quell™ Wearable Pain Relief Technology for Treatment of Chronic Pain. NeuroMetrix Inc, 2015
8. National Cancer Institute. SEER research data 1973- 2012dASCII text data: Surveillance, Epidemiology, and End Results (SEER) Program research data (1973-2012). www.seer.cancer.gov. Published April 15, 2015. Accessed February 10th 2016.
9. American Cancer Society. Cancer Facts & Figures 2015. Atlanta, GA: American Cancer Society.<http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf>. Accessed February 10th 2016

10. Schmidt BL, Hamamoto DT, Simone DA, Wilcox GL. Mechanism of cancer pain. *Mol Interv.* 2010;10(3):164-178.
11. Ellis A, Bennett DL. Neuroinflammation and the generation of neuropathic pain. *Br J Anaesth.* 2013;111(1):26-37.
12. Jensen MP. A neuropsychological model of pain: research and clinical implications. *J Pain.* 2010;11(1):2-12.
13. DeSantana JM, Walsh DM, Vance C, Rakel BA, Sluka KA. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Curr Rheumatol Rep.* Dec 2008;10(6):492-499.
14. Katz J, Rosenbloom BN. The golden anniversary of Melzack and Wall's gate control theory of pain: Celebrating 50 years of pain research and management. Katz J, Rosenbloom BN. **Pain** Res Manag. 2015 Nov-Dec;20(6):285-6.
15. Ainsworth L, Budelier K, Clinesmith M, et al. Transcutaneous electrical nerve stimulation (TENS) reduces chronic hyperalgesia induced by muscle inflammation. *Pain.* Jan 2006;120(1-2):182-187.
16. Somers DL, Clemente FR. Contralateral high or a combination of high- and low-frequency transcutaneous electrical nerve stimulation reduces mechanical allodynia and alters dorsal horn neurotransmitter content in neuropathic rats. *J Pain.* Feb 2009;10(2):221-229.
17. Chan CW, Tsang H. Inhibition of the human flexion reflex by low intensity, high frequency transcutaneous electrical nerve stimulation (TENS) has a gradual onset and offset. *Pain.* Feb 1987;28(2):239-253.
18. Dean J, Bowsher D, Johnson MI. The effects of unilateral transcutaneous electrical nerve stimulation of the median nerve on bilateral somatosensory thresholds. *Clin Physiol Funct Imaging.* Sep 2006;26(5):314-318.
19. Dailey DL, Rakel BA, Vance CG, et al. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain.* Nov 2013;154(11):2554-2562.
20. Sluka KA, Deacon M, Stibal A, Strissel S, Terpstra A. Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. *J Pharmacol Exp Ther.* May 1999;289(2):840- 846.
21. Leonard G, Goffaux P, Marchand S. Deciphering the role of endogenous opioids in high-frequency TENS using low and high doses of naloxone. *Pain.* Oct 2010;151(1):215-219.
22. Smith TJ, Coyne PJ, Parker GL, Dodson P, Ramakrishnan V. Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare") for chemotherapy-induced peripheral neuropathy. *J Pain Symptom Manage.* 2010;40(6): 883-891.

23. Pachman DR, Weisbrod BL, Seisler DK, et al. Pilot evaluation of Scrambler therapy for the treatment of chemotherapy- induced peripheral neuropathy. *Support Care Cancer*. 2015; 23(4):943-951.
24. Johnson MI. Transcutaneous Electrical Nerve Stimulation (TENS) and TENS-like devices: do they provide pain relief? *Pain Reviews*. 2001;8:121-158.
25. Johnson MI, Bjordal JM. Transcutaneous electrical nerve stimulation for the management of painful conditions: focus on neuropathic pain. *Expert Rev Neurother*. May 2011;11(5):735- 753.
26. Chen CC, Tabasam G, Johnson MI. Does the pulse frequency of transcutaneous electrical nerve stimulation (TENS) influence hypoalgesia? A systematic review of studies using experimental pain and healthy human participants. *Physiotherapy*. 2008;94:11-20.
27. Law PP, Cheing GL. Optimal stimulation frequency of transcutaneous electrical nerve stimulation on people with knee osteoarthritis. *J Rehabil Med*. Sep 2004;36(5):220-225.
28. Moran F, Leonard T, Hawthorne S, et al. Hypoalgesia in response to transcutaneous electrical nerve stimulation (TENS) depends on stimulation intensity. *J Pain*. Aug 2011;12(8):929-935.
29. Farrar JT, Young JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.
30. Younger J, McCue R, Mackey S. Pain Outcomes: A Brief Review of Instruments and Techniques. *Current pain and headache reports*. 2009;13(1):39-43.

25. Appendix

PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

Date: _____

Name: _____ **DOB:** _____

Chief Complaint (Presenting Problem): _____

Since beginning treatment at this facility, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your post-concussive condition?

Choose ONE.

- ☐ No change (or condition has gotten worse) (1)
- ☐ Almost the same, hardly any change at all (2)
- ☐ A little better, but no noticeable change (3)
- ☐ Somewhat better, but the change has not made any real difference (4)
- ☐ Moderately better, and a slight but noticeable change (5)
- ☐ Better and a definite improvement that has made a real and worthwhile difference (6)
- ☐ A great deal better and a considerable improvement that has made all the difference (7)

Patient's Signature: _____



EORTC QLQ-C15-PAL (version 1)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
2. Do you need to stay in bed or a chair during the day?	1	2	3	4
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
4. Were you short of breath?	1	2	3	4
5. Have you had pain?	1	2	3	4
6. Have you had trouble sleeping?	1	2	3	4
7. Have you felt weak?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
10. Have you been constipated?	1	2	3	4
11. Were you tired?	1	2	3	4
12. Did pain interfere with your daily activities?	1	2	3	4
13. Did you feel tense?	1	2	3	4
14. Did you feel depressed?	1	2	3	4

For the following question please circle the number between 1 and 7 that best applies to you

15. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Date: _____
Subject ID: _____

Short-form McGill Pain Questionnaire 2 (SF-MPQ-2)

For this questionnaire, I will provide you a list of words that describe some of the different qualities of pain and related symptoms. Please rate the intensity of each of the pain and related symptoms you felt during the past week on 0 to 10 scale, with 0 being no pain and 10 being the worst pain you can imagine. Use 0 if the word does not describe your pain or related symptoms. Limit yourself to a description of the pain related to your surgery or pelvic pain.

1. Throbbing pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
2. Shooting pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
3. Stabbing pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
4. Sharp pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
5. Cramping pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
6. Gnawing pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
7. Hot-burning pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
8. Aching pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
9. Heavy pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
10. Tender	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
11. Splitting pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
12. Tiring-exhausting	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
13. Sickening	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
14. Fearful	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
15. Punishing-cruel	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
16. Electric-shock pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
17. Cold-freezing pain	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
18. Piercing	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
19. Pain caused by light touch	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
20. Itching	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
21. Tingling or 'pins and needles'	none	0	1	2	3	4	5	6	7	8	9	10	worst possible
22. Numbness	none	0	1	2	3	4	5	6	7	8	9	10	worst possible

23. Present Pain Intensity (PPI) – Numerical Pain Rating Scale. On a scale from zero to ten, zero indicating no pain and ten indicating worst pain imaginable, rate your pelvic pain:

None	0	1	2	3	4	5	6	7	8	9	10	worst possible
------	---	---	---	---	---	---	---	---	---	---	----	----------------

24. Evaluative overall intensity of total pain experience. Please check (✓) the word that describes the pain in your pelvic area only.

☐ No pain ☐ Mild ☐ Discomforting ☐ Distressing ☐ Horrible ☐ Excruciating

Sleep Scale from the Medical Outcomes Study

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes.....1

16-30 minutes.....2

31-45 minutes.....3

46-60 minutes.....4

More than 60 minutes5

-
2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number
of hours per night:

--	--

How often during the past 4 weeks did you...

(Circle One Number On Each Line)

	All of the Time ▼	Most of the Time ▼	A Good Bit of the Time ▼	Some of the Time ▼	A Little of the Time ▼	None of the Time ▼
3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
4. get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
5. awaken short of breath or with a headache?	1	2	3	4	5	6
6. feel drowsy or sleepy during the day?	1	2	3	4	5	6
7. have trouble falling asleep?	1	2	3	4	5	6
8. awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
9. have trouble staying awake during the day?	1	2	3	4	5	6
10. snore during your sleep?	1	2	3	4	5	6
11. take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
12. get the amount of sleep you needed?	1	2	3	4	5	6

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Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), Measuring functioning and well-being: The Medical Outcomes Study approach (pp. 235-259). Durham, NC: Duke University Press.