Tivic Health Systems	Protocol: CP00003 ClearUP At-Home Pilot Study
STUDY PROTOCOL	
VERSION 1	DATE: 10.30.2018

SPONSOR:
Tivic Health Systems
750 Menlo Ave, #200
Menlo Park, CA 94025

STUDY SUMMARY:

Title	ClearUP At-Home Pilot Study
Purpose	To assess the feasibility of at-home use of ClearUP and collect data on the longitudinal safety and efficacy of ClearUP as a treatment for pain and congestion.
Study Design and Duration	A single-arm prospective study of 30 recruited subjects suffering from sinus pain. All subjects will use the ClearUP Sinus Pain Relief device, a device that uses microcurrent to stimulate nerve fibers passing from the sinus passages through various foramina to the facial skin. Subjects will read manufacturer's provided Instructions-For-Use (IFU's) and proceed to self-perform the treatment. Subjects will report on sinus symptoms before and after the first treatment. Subjects will also take the device home and use the device daily for four weeks. Self-report questionnaires for pain, congestion, and medication use will be completed weekly throughout the study.
Target Subject Population	30 subjects suffering from sinus pain
Subject Inclusion Criteria	• 18-71 years of age (inclusive) • Present with symptoms of sinus pain or facial pain in the forehead, periorbital, facial, or nasal region • Current pain score ≥ 5 (Numeric Rating Scale 0-10) • Frequency of sinus/facial pain at least twice weekly for 1 month • Able to read and understand English • Agree to participate in the study • Able and willing to provide Informed Consent
Subject Exclusion Criteria	• Do not meet Inclusion Criteria

	• Currently taking or recently taken any oral steroid medications in the last 90 days • Sinus surgery in previous 90 days • History of Chronic Migraine (≥ 15 headache days per month) • Pain location in the vertex, occiput, or temporal region of the skull or in mandibular region • Purulent rhinorrhea • Current dental infection • Cranial nerve pathology (trigeminal neuralgia, facial nerve paralysis, etc.) • Primary pain disorder (fibromyalgia, chronic regional pain syndrome, etc.) • Implanted electrostimulation devices including a pacemaker, a deep brain stimulator, or a cochlear implant
Study Endpoints	This study is intended to assess feasibility of at-home use of the ClearUP device and to generate data on the safety and efficacy of ClearUP as a treatment for sinus pain and congestion over four weeks.

CONTACTS

Sponsor

Tivic Health Systems

Menlo Park, CA 94025

750 Menlo Ave, #200

jennifer.ernst@tivic.com

650 454 0322

Principal Investigator:

Dr. Alan Goldsobel

Allergy and Asthma Associates of Santa Clara Valley Research Center
4050 Moorpark Ave. STE 6
San Jose, CA 95117
USA

1. BACKGROUND AND RATIONALE

Inflammation of the sinuses and nasal mucosa results in symptoms such as thick nasal mucus, tissue swelling, nasal congestion or obstruction, and pain and pressure in the face[1, 2]. Patients with sinus pain typically describe the quality of the pain as pressure[3]. Sinonasal inflammation can be caused by infection, allergies, air pollution, or structural problems in the nasal passages. Sinonasal inflammation is a common condition that affects all age groups and women are often more affected than men.

Tivic Health Systems Inc. (the Sponsor) intends to introduce a new Transcutaneous Electrical Nerve Stimulator (TENS) device named ClearUP Sinus Pain Relief. The device relieves sinus pain by applying micro-amp electrical stimulation to facial nerves around the sinuses. i.e., the regions around the nose and the supraorbital region of the eye.

References:

1. Seidman, M.D., et al., *Clinical practice guideline: Allergic rhinitis.* Otolaryngol Head Neck Surg, 2015. **152**(1 Suppl): p. S1-43.
2. Rosenfeld, R.M., et al., *Clinical practice guideline (update): Adult Sinusitis Executive Summary.* Otolaryngol Head Neck Surg, 2015. **152**(4): p. 598-609.
3. Cady, R.K., et al., *Sinus headache: a neurology, otolaryngology, allergy, and primary care consensus on diagnosis and treatment.* Mayo Clin Proc, 2005. **80**(7): p. 908-16.

2. Description of the ClearUP Sinus Pain Relief Device

ClearUP Sinus Pain Relief (Active Device)

ClearUP Sinus Pain Relief is a handheld micro-current TENS device used for the temporary relief of sinus pain. The device uses an average current that is several orders of magnitude smaller than that of previously cleared TENS devices used in the facial area. The design of ClearUP Sinus Pain Relief was optimized to provide transcutaneous nerve stimulation to the regional areas associated with the sinuses.

The pear-shaped device is held in the hand, with the rounded tip of the device applied to the facial skin in the region of the sinus passages. The tip is the active electrode of a monopolar design. The housing of the device serves as the return electrode. The hand holding the device completes the electrical path.

When the user turns the device on and presses the tip to the skin, the device lights up and initiates a low-frequency, pulsed AC circuit that is maintained at a constant current. The device uses the current to calculate the impedance in the path between the tissue at the tip and the hand in contact with the device.

If the calculated impedance is above an impedance threshold, the device is in "Detection" mode. Conversely, when the impedance falls below the impedance threshold, the device enters a "Treatment" mode. The impedance threshold is calculated dynamically by an adaptive algorithm that incorporates the measured parameters of the individual user.

The user is instructed to glide the tip of the device along the skin along the cheek, nose and under brow bone. When a low-impedance point is detected, the device signals the user via a slight haptic (vibration) feedback. The user is instructed to hold the device in place until the Treatment period has passed as indicated by cessation of the haptic indicator (approximately 7 seconds).

Once the Treatment period ends, the device resets to Detection mode. The user is instructed to glide the device along an indicated path until reaching the next low-impedance area.

The user may adjust the current setting of the device (low, medium, high) if they prefer more or less current intensity. The default setting for the device is low.

3. INDICATIONS FOR USE

The ClearUP™ Sinus Pain Relief device is to be used for the temporary relief of sinus pain.

4. STUDY OBJECTIVES

To assess the feasibility of at-home use of ClearUP and collect data on the longitudinal safety and efficacy of ClearUP as a treatment for pain and congestion.

5. STUDY DESIGN

This single-arm (N=30) open label study will be carried out at the Allergy and Asthma Associates of Santa Clara Valley Research Center (San Jose, CA) in collaboration with principle investigator Dr. Alan Goldsobel. Study subjects will be recruited from Dr. Goldsobel's allergy practice and from the surrounding community. Eligible subjects will complete informed consent and be enrolled into the study. Validated questionnaires will be used to quantify sinonasal symptoms including pain (numeric rating scale) and congestion (Congestion Quantifier 7), medication use, and user experience. Subjects will use the ClearUP device for five minutes during the study visit and then take the device home with them with instructions to use the device once daily and up to four times daily as needed, with each treatment lasting five minutes. Acute pain relief data will be collected after the first treatment (0-6 hours) and data on pain, congestion, and medication use will be collected weekly for four weeks. To facilitate a real-world pragmatic trial, subjects will be allowed to use medication during the study. Study visits will take place at enrollment and at 4 weeks.

Study Flow & Data Collection

Enrollment Visit

- Confirm eligibility & consent
- Subject Demographics
- Numeric Rating Scale for Pain (Worst, Best, Average over past week)
- Nasal Obstruction Symptom Evaluation (NOSE)
- Sino Nasal Outcome Test (SNOT22)
- Congestion Questionaire 7 (CQ7)
- Medication taken in previous week
- NRS before and 10 minutes, 1h, 2h, 4h, 6h after 5 minute ClearUP treatment (1h-6h collected on take-home worksheet)
- $50 compensation

Self-Report At Home– Weekly (end of week 1, 2, 3)

- Numeric Rating Scale for Pain (Worst, Best, Average over past week)
- Sino Nasal Outcome Test (SNOT22) – only week 2
- Congestion Questionaire 7 (CQ7)
- Medication taken in previous week

30 Day Visit

- Numeric Rating Scale for Pain (Worst, Best, Average over past week)
- Nasal Obstruction Symptom Evaluation (NOSE)
- Sino Nasal Outcome Test (SNOT22)
- Congestion Questionaire 7 (CQ7)
- Medication taken in previous week
- Subject Questionnaire
- Consent to be contacted for additional research
- $200 compensation

6. SUBJECT POPULATION

It is anticipated that at least 30 subjects will be recruited. Any subject that meets the inclusion/exclusion criteria may participate in the study.

7. INCLUSION/EXCLUSION CRITERIA

All subjects meeting the following inclusion criteria will be eligible to participate in this study.

a. Inclusion Criteria

To be included in this study, subjects MUST:

- 18-71 years of age (inclusive)
- Present with symptoms of sinus pain or facial pain in the forehead, periorbital, facial, or nasal region
- Current pain score ≥ 5 (Numeric Rating Scale 0-10)
- Frequency of sinus/facial pain at least twice weekly for 1 month
- Able to read and understand English
- Agree to participate in the study
- Able and willing to provide Informed Consent

b. Exclusion Criteria

- Do not meet Inclusion Criteria
- Currently taking or recently taken any oral steroid medications in the last 90 days
- Sinus surgery in previous 90 days
- History of Chronic Migraine (≥ 15 headache days per month)
- Pain location in the vertex, occiput, or temporal region of the skull or in mandibular region
- Purulent rhinorrhea
- Current dental infection
- Cranial nerve pathology (trigeminal neuralgia, facial nerve paralysis, etc.)
- Primary pain disorder (fibromyalgia, chronic regional pain syndrome, etc.)
- Implanted electrostimulation devices including a pacemaker, a deep brain stimulator, or a cochlear implant

8. STUDY PROCEDURES

All study procedures involving subject participation will be conducted according to good clinical practices (GCP) and in compliance with the principles enunciated in the Declaration of Helsinki. All study procedures will be performed at an Investigational Site, under the direction of an Investigator or designee, and at which this protocol will be approved by:

Solutions Institutional Review Board

22695 S. Highway 89
Yarnell AZ 86332

a. Subject Screening

Subjects suffering from sinus pain will be invited to participate and will score their pain level using the numeric rating scale. If they meet the inclusion criteria of a pain score ≥ 5 they will be entered into a Subject Screening log and assigned a unique subject ID number starting with 201. Using the ID number, subject information will be entered into a Subject Demographics log, the subject will sign an Informed Consent form, and the initial pain score will be recorded in the subject's Enrollment Pain Data sheet.

b. Randomization

Subjects will not be randomized.

c. Study procedure

After enrollment and informed consent procedures, subjects will fill out questionnaires related to demographics, sinus pain (numeric rating scale), congestion (congestion quantifier 7, nasal obstruction symptom evaluation), sinus symptoms (sinonasal outcome test 22), and medication use (medication diary). Then study subjects will read the instructions for use for ClearUP and self-administer a five minute treatment with the device. Subjects will fill record their numeric rating scale for pain after the first treatment at the following timepoints: 10 minutes, 1 hour, 2 hours, 4 hours, 6 hours. Subjects will be given the device and instructions for use and a study binder to take home with them. They will be instructed to use the device once daily and up to four times daily as needed for the four week duration of the study. Subjects will be asked to fill out the weekly questionnaires found in the study binder (see above Study Flow and Data Collection). Text message reminders will be sent to use the device daily and to fill out questionnaires weekly. At the four-week study visit, subjects will return their study devices, fill out questionnaires describing their symptoms in the final week of treatment, and respond to a questionnaire detailing their user experience. Compensation for the study will be $250 in the form of a Visa gift card.

d. Data analysis

All data will be tabulated. The difference between the symptom scores before and after treatment will be computed for each individual in the study.

An appropriate two-sided statistical test (paired t-test or repeated measure one-way ANOVA) will be used to assess the pre and post differences in symptom severity.

9. STUDY ENDPOINTS

This study is intended to assess feasibility of at-home use of the ClearUP device and to generate data on the safety and efficacy of ClearUP as a treatment for sinus pain and congestion over four weeks.

10. SPONSOR AND INVESTIGATOR OBLIGATIONS

a. IRB Review/Approval/Reporting

The final protocol and Informed Consent for this study will be reviewed and approved by the appropriate duly constituted Institutional Review Board (IRB) prior to the enrollment of subjects into the study. It is the responsibility of the Investigator to assure that all aspects of the institutional review are conducted in accordance with current United States Food and Drug Administration (FDA) regulations. The Sponsor must receive a letter documenting the IRB approval that specifically identifies the protocol by title, prior to initiation of the study.

After the completion or termination of the study, the Investigator will submit a final report to the IRB and to the Sponsor.

b. Informed Consent

It is the responsibility of the Investigator to assure that Informed Consent is obtained from each subject in accordance with current regulations. The content of the Informed Consent should conform to current ICH and FDA guidelines for the protection of human subjects, and/or to the specific IRB requirements.

The Informed Consent form must be in English, signed and dated by the subject and Investigator or designee.

Each subject will be given verbal and written information describing the nature and duration of the study. This shall take place under conditions where the subject has adequate time to consider the risks associated with his/her participation in the study. All subjects' questions must be answered adequately to ensure that they have the information they require to make an informed decision about participation in the study. The signed Informed Consent form will be filed in a study file along with all study forms.

Subjects must not be tested until they sign an Informed Consent form.

c. Data Reporting

Data reflecting subject experience during the Study will be reported to Tivic Health Systems Inc. or its designee (contract research organization). After reviewing all information, the Investigator must verify

the accuracy and completeness of all recorded data by signing and dating all Data Collection sheets prior to submitting them to the Sponsor.

At intervals during the study and at study completion, the Investigator must submit the following to the Sponsor or its designee:

- Eligibility Checklist
- Subject Demographics log
- Enrollment Pain Data sheet
- Subject Reminder Sheet
- Post-Visit Pain Data sheet
- Weekly Pain Data Sheet
- Congestion Quantifier 7
- Medication Diary
- Sinonasal Outcome Test 22
- Nasal Obstruction Symptom Evaluation
- Subject Questionnaire
- Consent to Be Contact

The forms above will constitute the original study record. They will be filled out manually by study staff. If an entry requires change, the correction will be made as follows:

- Draw a single line through the incorrect entry.
- Enter data, date, and initial the change ("white-out", erasure, or any form of obliteration of data is not permitted under any circumstances).

Neither the Sponsor nor its designee can interpret a blank answer as "none" or "N/A"; therefore, all fields must be completed. If data are not available, a straight line should be drawn through all applicable fields and unused pages, dated and initialed to indicate there was no omission.

All supportive documentation submitted to Tivic Health Systems Inc. must be clearly identified with the study and subject ID number. Any personal information, including subject name, address, phone number, or social security number must be removed or rendered illegible to preserve individual confidentiality.

d. Data Retention

The Investigator will maintain adequate records for the study including the Subject Demographics log, Data Collection sheets, Informed Consent forms, information regarding discontinued subjects, and other pertinent data.

All records must be retained by the Investigator according to FDA requirements. In the United States, records must be retained for a period of two (2) years after FDA approval/clearance of a system. The Investigator will contact Tivic Health Systems Inc. for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records.

e. Protocol Deviations/Amendments

The Investigator shall not deviate from the protocol without documented approval from the Sponsor. Any significant changes or deviations in the protocol will be made as an amendment to the protocol and must be approved in writing by the IRB and by the Sponsor prior to being implemented. Unless the Sponsor has consented to any such deviation or change in writing, the Sponsor will not assume any resulting responsibility or liability.

Amendments to the protocol will be subject to the same requirements as the original protocol, with the exception of administrative amendments. The Sponsor will submit a protocol amendment to the Investigator and to the IRB for any change in the protocol that significantly affects the safety of subjects or scope of the investigation.

Administrative amendments may be made by mutual agreement between the Investigator and the Sponsor and will be documented in writing with copies to both the Investigator and the Sponsor.

f. Study Monitoring

The Investigator must agree to allow the Sponsor or its representatives to periodically monitor and audit study data and forms. Monitoring visits are to be arranged at mutually convenient times during the study. Upon completion of the study, all records will be thoroughly reviewed for accuracy and completeness. Monitoring visits provide the Sponsor or its representatives with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of the forms, to assure that all protocol requirements and applicable FDA regulations and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

The monitor will ensure that the subjects entered into the study meet the protocol entry criteria. The monitor will verify that the procedures and practices defined in the protocol are all performed and accomplished in the specified time frame.

g. Adverse Event Reporting

A significant adverse event (SAE) is one that has a serious adverse effect on the health or safety of a subject, or causes any life-threatening problem or death of the study subject.

All SAEs should be recorded by the Investigator and reported by the Investigator to the Sponsor and to the IRB the next business day after the Investigator becomes aware of the SAE.

The Sponsor will collect adverse effects information and will report serious and unanticipated adverse effects to the FDA. The Sponsor will terminate the study within five working days if the Sponsor determines that the adverse system effects present an unreasonable risk to subjects (21 CFR 812.46(b)(2)).

An adverse event (AE) during a clinical evaluation is "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device." It is not dependent on whether the event is considered to be related to the investigational product or the study. An adverse event includes events not seen at the beginning of the study, or worsened if present at the beginning.

All AEs observed by the Investigator or reported by the subject will be documented (including all symptoms) and included in the study file.

h. Potential Benefits

There is no guaranteed benefit to a subject for participation in this study.

11. COST

There will be no additional charge to subjects for any study procedures.

12. COMPENSATION

Subjects will be compensated for study participation. There will also be compensation to study clinical site.

All Sponsors' supplies will be provided to the sites and to the subjects at no charge. Subject medications will not be covered by the Study Sponsor.

13. STUDY QUALITY CONTROL AND QUALITY ASSURANCE

a. Site Training

The Investigator is required to attend a Sponsor's training session which will be conducted at a site initiation visit or other appropriate training sessions. Training will include, but not be limited to the procedures with which to address subjects, the protocol plan, the completion of the various forms and

the responsibilities of study staff. All Investigators or study staff that are trained must sign a Staff Training log. No Investigator or study staff will perform any study-related procedures prior to being trained and prior to signing a Staff Training log.

At the initiation of the study, the Sponsor or designee will visit the site where the study is conducted. The Sponsor will ensure that clinical study staff are informed and understand the clinical study requirements.

b. Compliance to Standards and Regulations

The Sponsor is responsible for obtaining and reviewing copies of IRB approvals, and ensuring that the study is conducted in compliance with the protocol, Code of Federal Regulations, the Declaration of Helsinki and applicable local regulatory requirements, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained.

The Investigator shall ensure that all work and services described herein shall be conducted in accordance with the highest standards of medical and clinical research practice. The Investigator will provide copies of the protocol to all co-Investigators or other staff responsible for study conduct.

The Investigator shall ensure that all serious adverse events will be reported to the Sponsor within 24 hours.

Regulatory documentation includes those documents that must be submitted, reviewed and approved by the Sponsor before subject enrollment can begin at the clinical site. These documents function to demonstrate compliance of the Investigator and Sponsor with regulatory requirements.

c. Quality Assurance Audit

In the event that an Investigator is contacted by a Regulatory Agency in relation to this study, the Investigator will notify the Sponsor immediately. The Investigator or his designee must be available to respond to reasonable requests and audit queries made during an audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (e.g., Form FDA 483, Inspectional Observations, and warning letters).

14. PUBLICATION POLICY

The data and results from this study are the sole property of the Sponsor. The sponsor shall have the right to access and use all data and results generated during the clinical study. The Investigator will not use the study related data without the written consent of the Sponsor for any other purpose other than for study completion or for generation of publication material. The Sponsor must approve all materials for publication prior to submission.

15. CONFIDENTIALITY

The Sponsor will not release the subject's private and personal information.

This study protocol, documentation data, and all other information generated, will be held in strict confidence by the Investigator and their representatives. No information concerning the study or the data will be released to any unauthorized third party without prior written approval by the Sponsor.

No subject names, medical record numbers, or other personally identifying information will be used as part of the study. Data Collection forms will not contain confidential information linking the outcome result to a subject. Only the study site will have the information that links a subject to his/her identifying information. Subjects will only be referred to by using their unique Subject ID number.