A STUDY OF SAFETY AND EFFICACY OF TRANSCUTANEOUS AFFERENT PATTERNED STIMULATION (TAPS) FOR REDUCTION OF ACTION TREMOR IN PARKINSON'S DISEASE (PD)

PROTOCOL PD-02
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A study of safety and efficacy of Transcutaneous Afferent Patterned Stimulation (TAPS) for reduction of action tremor in Parkinson's Disease (PD)

PD-02

SPONSOR SIGNATURE PAGE

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CLINICAL STUDY SYNOPSIS

Study Objective	
Title	A study of safety and efficacy of Transcutaneous Afferent Patterned Stimulation (TAPS) for reduction of action tremor in Parkinson's Disease (PD)
Study Device	Cala Trio
Objective	Demonstrate safety and efficacy of TAPS delivered by the Cala Trio™ device as a treatment for action tremor in subjects with Parkinson's disease hand tremor.

Study Design Elements	
Study Design	Single arm study
Overview of Study Visits and Procedures	This study will include both subjects on levodopa and subjects taking other Parkinson's medications/unmedicated for Parkinson's. Subjects will be screened for eligibility and fitted with a Cala Trio device. Due to COVID-19 social distancing requirements, visits requiring physician or subject rated assessments will be conducted via telemedicine (i.e., video call). During Visit 1 (Day -7), enrollment will consist of subject eligibility/screening using clinician rated UPDRS assessments. During Visit 2a (Day -1), subjects will receive device training and calibration instructions. During Visit 2b (Day 0), UPDRS assessments and ability to conduct ADLs will be assessed pre and post stimulation session. Visits 2a and 2b may be combined into a single visit. Subjects will use Cala Trio at home for a period of 4 weeks (Day 1- Day 28). During Visit 3 (Day 28), the subjects will exit the study after a UPDRS and ADLs assessment pre and post stimulation session.
Efficacy Assessments	• Primary: Within subject comparison of tremor power before stimulation to after stimulation in dominant arm • Secondary: Within subject comparison of ADLs and UPDRS across Visits 1-3
Safety	The safety of the peripheral nerve stimulation will be characterized by the incidence of device and therapy-related adverse events
Number of Subjects	Up to 60 subjects
Number of Sites	1 site
Study Participation	The length of study participation is up to 6 weeks

Subject Population	

Inclusion Criteria	Prospective subjects must meet all of the following criteria to be eligible for study participation:
	
	• Must be ≥22 years of age
	• Competent and willing to provide written, informed consent to participate in the study
	• Clinically significant postural tremor as defined by:
	  o Dominant hand/arm exhibiting postural tremor ≥ 2 (while in the off state) as assessed by the MDS-UPDRS postural tremor score
	• Stable dose of Parkinson's disease medications, if applicable, for 30 days prior to study entry
	• Willing to comply with study protocol requirements including:
	  o Having the ability to do telemedicine or video calls for study visits
	  o remaining on a stable dosage of Parkinson's medications, if applicable, during the duration of the study
	  o no significant caffeine consumption within 8 hours of study visits

Exclusion Criteria	Prospective subjects who meet any of the following criteria are not eligible for enrollment in this study: • Implanted electrical medical device, such as a pacemaker, defibrillator, or deep brain stimulator • Suspected or diagnosed epilepsy or other seizure disorder • Swollen, infected, inflamed areas, or skin eruptions, open wounds, or cancerous lesions of skin at stimulation site • Peripheral neuropathy affecting the tested upper extremity • Presence of any other neurodegenerative disease or dementia. These may include: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Alzheimer's disease. • Botulinum toxin injection for hand tremor within 6 months prior to study enrollment • Are participating or have participated in another interventional clinical trial in the last 30 days which may confound the results of this study, unless approved by the Sponsor • Significant caffeine consumption within 8 hours of study enrollment, which may confound the results of the study, where significant caffeine is considered more than 95 mg (equivalent to a cup of coffee). • Subjects unable to communicate with the investigator and staff • Any health condition that in the investigator's opinion should preclude participation in this study • Pregnancy or anticipated pregnancy during the course of the study

Study Contacts	
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1.0 Introduction

Idiopathic Parkinson's disease (PD) is characterized by the cardinal motor signs and symptoms of rest tremor, bradykinesia and muscle rigidity. The perception of most PD clinicians is that of these, bradykinesia is the most disabling symptom in early and moderate PD (balance/gait difficulties and cognitive impairment are almost universally agreed to be the most disabling feature in more advanced PD). The classic teaching of treatment for PD tremor is that because it is predominant at "rest" and often resolves with movement and when reaching for a target, it is not functionally very disabling and therefore should not be a focus of therapeutic outcomes. However, for a substantial number of people with PD, the postural and kinetic components of their tremor are indeed disabling.

Further, of all of the cardinal motor features of PD, tremor is the most resistant in response to dopaminergic therapies [1-2]. For many with disabling PD tremor, the only effective therapeutic alternative is Deep Brain Stimulation (DBS), which is a highly invasive procedure.

The Cala Trio device may offer patients with PD a novel non-pharmacological, non-invasive alternative, in the form of stimulation of peripheral nerves, to aid in action hand tremor relief. This highly innovative form of therapy will have important health, quality of life, and economic benefits for PD patients.

1.1 Scientific Background

Transcutaneous electrical nerve stimulation (TENS) is a form of noninvasive stimulation of peripheral nerves that has been shown to be safe and effective in treating various pain syndromes [3-6]. The mechanism of TENS is thought to be modulation of sensory input at the level of the spinal cord or brain.

Traditional TENS and DBS use continuous, fixed-frequency stimulation; however, accumulating evidence suggests that patterned electrical stimulation may improve the therapies' selectivity and effectiveness [7-10]. There is also specific evidence supporting the use of an alternating stimulation pattern for tremor reduction [11]. Peripheral nerve stimulation at the wrist activates neural networks similar to those responsible for the therapeutic mechanism of DBS in suppressing tremor [12-13]. Furthermore, recent literature suggests that the timing of stimulation in relation to the tremor is critical for effective tremor suppression [14-15].

Based on this research, Cala Health developed the Cala Trio device, which delivers alternating bursts of transcutaneous electrical stimulation to the radial and median nerves at the wrist. The stimulation is tremor-customized, meaning that each nerve receives bursts of stimulation at the patient's measured tremor frequency. This new form of non-invasive peripheral nerve stimulation is called transcutaneous afferent patterned stimulation (TAPS). TAPS is designed specifically to relieve hand tremor symptoms in patients with essential tremor (ET). The purpose of this study is to demonstrate the safety and efficacy of TAPS' utility in the new indication of PD.

2.0 Device Description

2.1 Intended Use

The Cala Trio device (Figure 1) is an investigational device designed for the delivery of Transcutaneous Afferent Peripheral Stimulation (TAPS). The device is to be used only in accordance with the approved investigational plan and requires informed consent.

2.1.1 Cala Trio Device

The Cala Trio device is designed to deliver TAPS to the median and radial nerves of the wrist on which it is worn. The device system includes three components listed below; details about these components follow.

Stimulator – a body worn stimulator which snaps into a wristband to apply a customized stimulation pattern to the median and radial nerves of an individual;

Band – a wristband with embedded multi-use electrodes which conduct the stimulation. Unlike standard hydrogel electrodes, the multi-use electrodes are not limited to single use and may be repeatedly used by the same subject;

Base station – a charging base station which charges the device and may upload device data to a secure cloud platform.

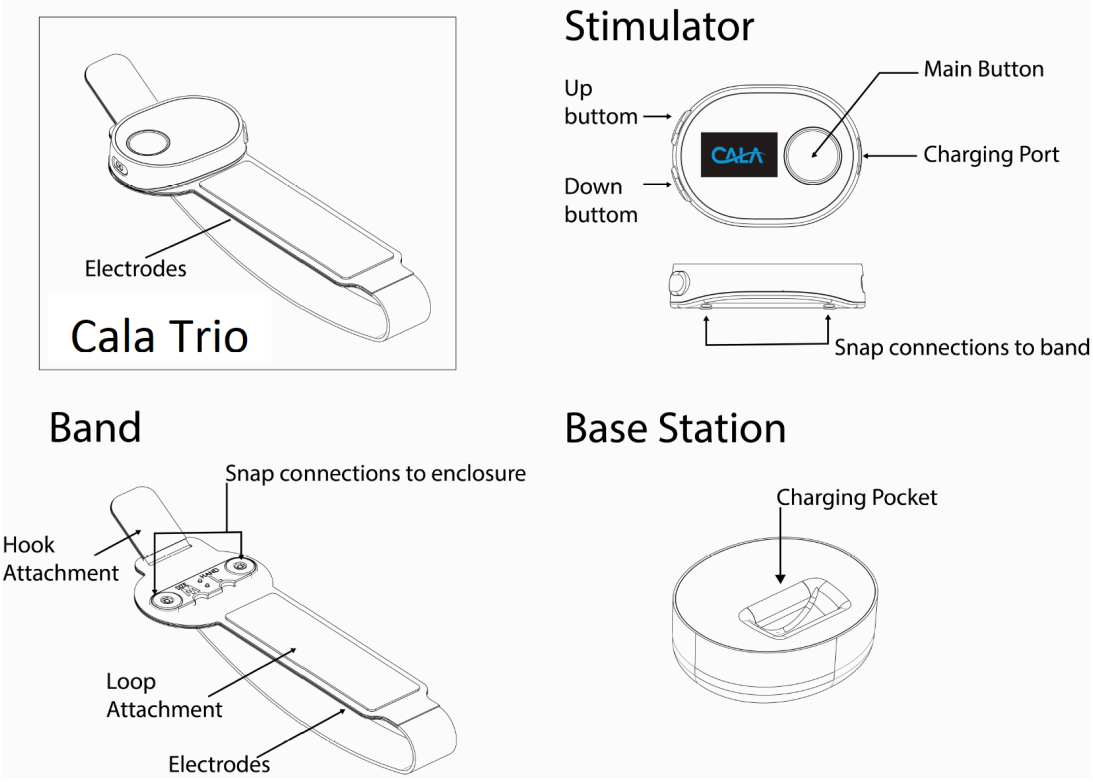

Figure 1. Cala Trio device components

2.1.2 Stimulator

The stimulator contains the electronics for providing TAPS and was designed with careful considerations of use by subjects with hand tremors. There are 3 easy-to-press buttons (Figure 1) on the stimulator that are used for calibration and stimulation amplitude adjustment, among other functions. Text prompts, stimulation delivery parameters, and other messages are provided on a full color display to provide instructions and stimulation delivery information to the clinician and subject throughout device use. A countdown timer automatically terminates the delivery of stimulation after a 40-minute treatment session. The stimulator is powered by a rechargeable battery, which can be recharged through the base station (see additional details below). The stimulator produces charge-balanced, current-controlled, biphasic, square waveforms. The duration of the primary (depolarizing) phase is 300 μsec, the frequency is 150 Hz, and the maximum current is 8 mA. The current is delivered to alternating electrode pairs in the band that target the median and radial nerves of the subject. The stimulation alternates between electrode pairs at the subject's tremor frequency (4 – 12 Hz), which is measured during a calibration procedure while the subject performs a tremor-inducing task. The tremor frequency is measured by motion sensors contained within the stimulator which gather kinematic data.

2.1.3 Band

Bands are constructed from a microfiber material with connectors to interface with the stimulator and a Velcro fastener to comfortably secure the device to the subject's wrist, much like a wristwatch.

There are multiuse electrodes are embedded in the band. The electrodes allow for good electrical conduction to the subject's skin. Unlike standard hydrogel electrodes, the electrodes are not limited to single use and may be repeatably used by the same subject for up to 90 consecutive days.

The electrodes are spaced at appropriate intervals around the circumference of the band in order to target the median and radial nerves properly. To accommodate a broad distribution of wrist sizes, the band has three sizes (small, medium, and large). The band is also right or left-handed to target the appropriate nerves of the prescribed hand with tremor.

2.1.4 Base Station

The base station is supplied with the Cala Trio device. For safety considerations, the Cala Trio device is designed such that it cannot be mechanically connected to the base station when it is worn by a subject (e.g., during stimulation delivery). The Cala Trio device is charged through the base station, which may be connected to a secure cloud platform which stores device data (e.g. kinematic data and usage information).

2.2 Instruction for Use and Labeling

The Cala Trio device will be used in accordance with its instructions for use.

The labeling on the Cala Trio device includes the statement, "CAUTION: Investigational Device. Limited by United States law to investigational use", as required by United States federal regulations.

3.0 Study Design

3.1 Overview

This is a single arm study done involving telemedicine visits and a home use period. Subjects will be seen for up to 4 telemedicine visits and will have a 4 week treatment period at home. During the treatment period, subjects will be asked to stimulate their dominant hand at home 2 times per day, preferably at the same time every day, measuring kinematics before and after every therapy session.
This study will include both subjects on levodopa and subjects taking other Parkinson's medications/unmedicated for Parkinson's.

3.2 Study Objectives

The study objective is to demonstrate safety and efficacy of TAPS delivered by the Cala Trio™ device as a treatment for action hand tremor in subjects with Parkinson's disease.

3.3 Inclusion Criteria

Prospective subjects must meet all of the following criteria to be eligible for study participation:

- Must be ≥22 years of age
- Competent and willing to provide written, informed consent to participate in the study
- Clinically significant postural tremor as defined by:
    - Dominant hand/arm exhibiting postural tremor ≥ 2 (while in the off state) as assessed by the MDS-UPDRS postural tremor score
- Stable dose of Parkinson's disease medications, if applicable, for 30 days prior to study entry
- Willing to comply with study protocol requirements including:
    - remaining on a stable dosage of Parkinson's medications, if applicable, during the duration of the study
    - no significant caffeine consumption within 8 hours of study visits
    - Having the ability to do telemedicine or video calls for study visits

3.4 Exclusion Criteria

Prospective subjects who meet any of the following criteria are not eligible for enrollment in this study:

- Implanted electrical medical device, such as a pacemaker, defibrillator, or deep brain stimulator
- Suspected or diagnosed epilepsy or other seizure disorder
- Swollen, infected, inflamed areas, or skin eruptions, open wounds, or cancerous lesions of skin at stimulation site
- Peripheral neuropathy affecting the tested upper extremity
- Presence of any other neurodegenerative disease or dementia. These may include: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Alzheimer's disease.
- Botulinum toxin injection for hand tremor within 6 months prior to study enrollment
- Are participating or have participated in another interventional clinical trial in the last 30 days which may confound the results of this study, unless approved by the Sponsor

- Significant caffeine consumption within 8 hours of study enrollment, which may confound the results of the study, where significant caffeine is considered more than 95 mg (equivalent to a cup of coffee).
- Subjects unable to communicate with the investigator and staff
- Any health condition that in the investigator's opinion should preclude participation in this study
- Pregnancy or anticipated pregnancy during the course of the study

3.5 Study Assessments

The following assessments will be done:

Subset of Activities of Daily Living (ADLs)
- Telemedicine, supervised and subject rated
- At home, instructed and subject rated

UPDRS Part III assessment
- Telemedicine, modified Part III (tremor tasks only)

CGI-S, I/PGI-S, I
- *Clinical Global Impression of Severity (CGI-S) & Improvement (CGI-I):* The investigator or designee will rate the subject's overall tremor severity & improvement.
- *Patient Global Impression of Severity (PGI-S) & Improvement (PGI-I):* The subject will self-assess their overall tremor severity & improvement.

Kinematic measurements performed with the Cala Trio device with motion sensors.

3.6 Safety

The safety of the peripheral nerve stimulation will be characterized by the incidence of device and therapy-related adverse events.

For this study, transient skin redness and/or itchiness lasting approximately less than 30 minutes will not be considered an adverse event. Similarly, transient discomfort with stimulation will not be considered an adverse event; however, persistent pain from stimulation will be considered an adverse event. For a complete list of potential risks to the subject see Section 5.2.2.

3.7 Blinding

Subjects and investigators/raters will not be blinded.

3.8 Sample Size

Up to 50 subjects will be enrolled.

3.9 Study Design Schematic

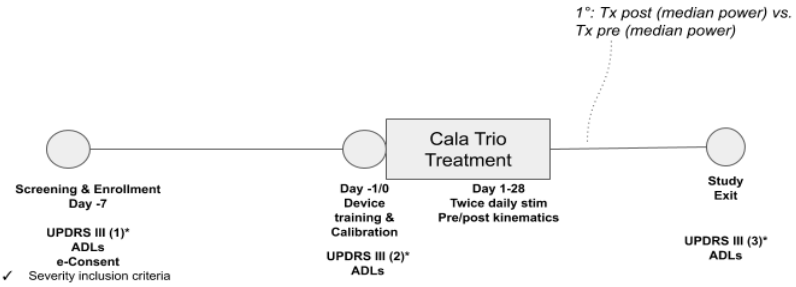

Figure 2. Study schematic of the study design.

3.10 Subject Recruitment

The study site may use several methods to identify and recruit potential subjects. These methods may include, but are not limited to, evaluation of subjects from their existing clinical practice, referrals from other physicians, review of available databases, or direct subject recruitment via advertising (with prior review and approval from Sponsor and reviewing IRB).

3.11 Pre-Screening/Scheduling

Prospective subjects may be pre-screened for the inclusion/exclusion criteria through an IRB approved script. The subject will be informed that they do not have to answer any questions they would not like to answer. If the subject appears to meet the inclusion/exclusion criteria and chooses to participate, they will be scheduled for a screening visit via telemedicine. Once subject is scheduled for a screening visit, they will be asked to hold their last dose of their Parkinson's medications prior to the visit.

3.12 Informed Consent

When a prospective subject has been identified and prior to beginning protocol-mandated testing, the study will be presented to them for consideration. The subject will be given adequate time to have their questions answered and to carefully consider participation. If, after understanding the purpose, potential risks and benefits, and requirements of the study, as well as their rights as a research subject, the individual agrees to participate, informed consent will be obtained. Informed consent will be documented in the subject's study records.

3.13 Screening

Following obtaining informed consent, potential subjects will undergo the following evaluations in order to ensure the subjects meet all of the inclusion criteria and none of the exclusion criteria:

- **Document current Parkinson's disease medications and medicine schedule**
- **Tremor Severity**: MDS-UPDRS Part III will be performed.
- **Medical History**: A brief medical history will be conducted to evaluate prior and existing medical conditions that may exclude individuals from the study. No medical records will be used for this study, so all eligibility criteria will be based upon self-

reported information from each subject and in-person verification by qualified study staff.

Subjects that don't meet all of the inclusion criteria and meet any one of the exclusion criteria will be considered screen fails.

3.14 Enrollment

Prospective, eligible subjects are considered officially enrolled in the study after they have signed the informed consent, completed the screening stage, and are confirmed to satisfy all protocol-mandated inclusion and exclusion criteria. If a prospective subject chooses to withdraw during or just after the screening stage but before they begin use of the Cala Trio, they will be considered a screen fail and exited from the study; they will not be counted as enrolled.

3.15 Visit 1

Subjects will be reminded to be in the *off* state, i.e. to skip their last dose of PD medication, prior to their telemedicine Visit 1. The following assessments will occur:

- Screening activities including medication review and medical history. No medical records will be used for this study, so all eligibility criteria will be based upon self-reported information from each subject and verification by qualified study staff.
- Tremor assessments (while in the *off* state) including:
    - Modified MDS Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS) to confirm eligibility will be rated by the PI
    - Bain & Findley Activities of Daily Living (ADL) upper limb subset score will be rated by the subject based on their recall of the previous week (no props will be used)
- Demographic information, Parkinson's clinical characteristics, and wrist size and handedness will be collected based on self-reported information from subjects.

Once a subject has been confirmed to be eligible for the study, a device kit containing a stimulator, base station and band will be shipped directly to the subject's home ahead of Visit 2.

3.16 Visit 2

3.16.1 Visit 2a

Once a subject has received the device kit, device training will occur via telemedicine, as follows:

3.16.1.1.1 Positioning and Fastening Cala Trio

Prior to device positioning, subjects should dampen the wrist of the prescribed hand to ensure good connection between the electrodes and wrist. Subjects should position the device on the prescribed hand such that the electrodes are positioned over the median and radial nerves, and securely tighten the band.

3.16.1.1.2 Device Calibration

To calibrate the Cala Trio device, subjects will perform a series of postural hold tremor tasks, in which the device measures the subject's tremor frequency and sets the stimulation burst frequency based on the measured tremor frequency.

For the purposes of this study, only the outstretched postural hold tremor task will be used.

3.16.1.1.3 Setting Stimulation Intensity

The subject will set the stimulation intensity to an amount they can comfortably tolerate while doing light activities. Paresthesia should be perceived in the parts of the hand and/or fingers innervated by the median and radial nerves. The stimulation intensity selected during the initial amplitude calibration is saved on the device for subsequent sessions. The subject can decrease or turn off the stimulation at any point in time, and may adjust their stimulation intensity from session to session to maintain the minimum paresthesia threshold.

3.16.1.1.4 Device Training

During the course of the visit, study personnel will instruct the subject on proper use of the device. Subjects must demonstrate competence to operate the device and comprehension of the instructions for use prior to completing the training.

3.16.2 Visit 2b

Once a subject is trained on the device, the subject will receive a single 40-minute therapy session with their Cala Trio. The subject will be asked to not stimulate at least 8 hours prior to this visit. The following assessments will be made prior to the therapy session and again immediately post the therapy session:

- Tremor assessments (while in the *off* state) including:
  - Modified MDS Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS) be rated by the PI
  - Bain & Findley Activities of Daily Living (ADL) upper limb subset score will be rated by the subject. The ADL assessment will be performed using the subject's own household props
- CGI-S, I/PGI-S, I
  - Clinical/Patient Global Impression of Severity (CGI-S/PGI-S): The investigator or designee (CGI) and Patient (PGI) will rate the overall tremor severity prior to stimulation
  - Clinical/Patient Global Impression of Improvement (CGI-I/PGI-I): The investigator or designee (CGI) and Patient (PGI) will rate the overall tremor improvement following stimulation

Additionally, the Cala Trio will direct the subject to perform the outstretched postural hold tremor tasks before and after the stimulation session to measure tremor power. Finally, subjects will input their Patient Session Impression of Improvement (PSI-I) rating on the device after the stimulation session

Visits 2a and 2b may be combined into a single Visit 2.

3.17 Home-Usage

The home use portion of the study will last 4 weeks. It will include:

- 2 stimulation sessions/day preferably at the same time every day-recommended as one in the morning and one in the evening.

- Motion Data on device before and after each stimulation session. Cala Trio will direct the subject to perform postural hold tremor tasks before and after the stimulation session to measure tremor power. Additionally, subjects will input their Patient Session Impression of Improvement (PSI-I) rating on the device after the stimulation session

- Weekly Bain & Findley Activities of Daily Living (ADL) upper limb subset score will be rated by the subject based on their recall of the previous week (no props will be used)

- Device factory reset of the Cala Trio will occur on Day 14 of treatment via a call with study staff

3.18 Visit 3/Study exit

Subjects will be reminded to be in the *off* state, i.e. to skip their last dose of PD medication, prior to their telemedicine Visit 3/Study exit. The subject will be asked to not stimulate at least 8 hours prior to this visit. The subject will receive a single 40-minute therapy session with their Cala Trio. The following assessments will be made prior to the therapy session and again immediately post the therapy session:

- Tremor assessments (while in the *off* state) including:
    - Modified MDS Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS) be rated by the PI
    - Bain & Findley Activities of Daily Living (ADL) upper limb subset score will be rated by the subject. The ADL assessment will be performed using the subject's own household props
- CGI-S, I/PGI-S, I
    - Clinical/Patient Global Impression of Severity (CGI-S/PGI-S): The investigator or designee (CGI) and Patient (PGI) will rate the overall tremor severity prior to stimulation
    - Clinical/Patient Global Impression of Improvement (CGI-I/PGI-I): The investigator or designee (CGI) and Patient (PGI) will rate the overall tremor improvement following stimulation

- Product/preference survey

- Subjects will return all study materials with provided shipping packages

A factory device reset and re-calibration may be required if the device does not prompt a tremor task measurement of postural hold prior to starting the stimulation session.

All subjects will be informed of their right to withdraw from the clinical study at any time without penalty or loss of benefits. The Investigator may prematurely discontinue any subject from the study if the Investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject.

3.19 Subjects Compensation

In order to compensate subjects for their time and effort, they will be paid an amount as listed on the site-specific Informed Consent Form (ICF).

4.0 Schedule of Assessments

The following table outlines the schedule of assessment for subjects throughout the entire duration of the study.

Table 1. Schedule of Assessments

	Assessment	Visit 1 (screening/ enrollment)	Visit 2a/b (device calibration/ training)	Home Use	Visit 3 (Study Exit)	After device is returned to Cala
	Time	**Day -7**	**Day -1/0 (+ 7 days)**	**Days 1-28**	**Day 28 (+ 7 days)**	**N/A**
PI or designee	Informed Consent	X				
	Medical History & Demographics	X				
	Medication Review	X				
	UPDRS modified Part III	X				
	Confirmation of Subject Eligibility	X				

	UPDRS modified Part III (pre/post stim)		X		X	
	CGI-S/I		X		X	
Cala	Device Calibration & Training		X			
Cala	Final device upload and device unassignment followed by factory reset			Factory reset on Day 14		X
Subject	Stimulation & PSI-I		X	2x per day	X	
Subject	Kinematics		Pre/Post stim	Pre/Post stim	Pre/Post stim	
Subject	B&F ADLs (recall)	X		1x per week	X	
Subject	B&F ADLs (pre/post stim)		X		X	
Subject	PGI-S/I		X		X	
Subject	Product Survey				X	
ALL	Adverse Events	X	X	X	X	

5.0 Risk and Benefit Assessment

5.1 Justification for the Study

While there are medications available to Parkinson's disease patients, they are not always effective in treating hand tremor. Another common treatment option is DBS, which, while effective, is highly invasive and risky. Therefore, effective alternative, non-pharmacologic treatment for Parkinson's disease may prove to be of value. The Cala Trio is a treatment alternative that is non-invasive, reversible, and potentially lower risk than currently available therapies.

5.2 Description and Analysis of All Potential Risks to Subjects

5.2.1 Risk Categories

Cala Health believes the investigational Cala Trio device and this study are *nonsignificant risk* as defined by the US IDE regulations (21 CFR 812).

5.2.2 Potential Risks and Protection against Risks

5.2.2.1 Potential Risks

The risks associated with the Cala Trio device are similar to those risks observed in the routine clinical use of commercially available transcutaneous electrical nerve stimulators (TENS devices) or cutaneous-placed electrodes. Cala Health's previous clinical study of a similar device showed a 2% chance of significant and persistent skin irritation (including redness, itchiness, and/or swelling), a 1% chance of stinging pain in the wrist, and a 1% chance of a feeling of weakness in the wrist. All incidences resolved without treatment or sequelae, and there were no serious adverse events.

Possible minor risks/adverse reactions that may occur with the use of the Cala Trio device and in this study are:

- Discomfort with stimulation (e.g. stinging, sensation of weakness, etc.)
- Allergic reaction to electrodes or other materials

- Skin irritation, including redness and/or itching

Possible adverse reactions that are more serious, but less likely to occur, with the use of the Cala Trio device and in this study are:

- Signs of significant skin irritation, sores, electrical burns or lesions at the site of stimulation
- Significant and persistent increase in muscle tightness or stiffness
- A feeling of chest pressure during stimulation
- Swelling of the arm, wrist, or hand

5.2.2.2 Protection against Risks:

The Cala Trio device will be used in the clinical study in accordance to the instructions for use provided with the investigational device. The instructions for use disclose the above risks and appropriate actions to take if these events should occur (e.g., stop using the device, notify the investigator, etc.).

Some subjects may find the tingling sensation from the stimulation to be unpleasant. To mitigate this risk, subjects will always have control over the stimulation level and may reduce or discontinue a stimulation level at any point in time.

To further minimize risk, subjects will be trained on device usage by a study staff member prior to using the device at-home and must demonstrate ability to successfully operate the device.

To mitigate the chance of adverse events occurring, all subjects participating in the study are evaluated and monitored during the study.

The relatively low current ($\leq$8 mA) electrical stimulation administered in this study is applied to the wrist, away from vital organs such as the heart. Therefore, this study does not pose any electrical safety hazard to the subject.

5.2.3 Minimization of Risks

5.2.3.1 Design Considerations

Cala Health has designed the Cala Trio device to minimize the risk posed to study subjects. The stimulator pulses are safe, observe charge delivery thresholds and safeguards, and are within the range of those used clinically for TENS devices [24]. The Cala Trio device delivers lower levels of energy than many commercially available transcutaneous stimulation devices, so Cala Health expects fewer potential complications and risks for the Cala Trio device.

5.2.3.2 Stimulation- current unable to be delivered

If the Cala Trio device were to malfunction and electrical current could not be delivered, this would not present a potential for serious risk to the health, safety or welfare of the subject. The effect would be that the subject would not receive stimulation and would require returning the malfunctioning device to the study site.

5.3 Potential Benefits

The subject's hand tremor may improve while in this study; however, this will not be guaranteed or promised to a subject.

5.4 Alternatives for Participation

Subject participation in this study is voluntary. Should the subject elect not to participate, alternatives to participation include medications and/or surgical options.

6.0 Clinical Event Definitions and Reporting

6.1 Definitions

6.1.1 Adverse Event

An AE 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.

6.1.2 Adverse Event Rate

The adverse event rate is defined as percentage of subjects who experienced an adverse event.

6.1.3 Serious Adverse Event

A SAE is an adverse event that either:

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted in:
- A life-threatening illness or injury
- A permanent impairment of a body structure or a body function
- In-subject hospitalization or prolonged hospitalization
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death or a congenital abnormality of birth defect.

6.1.4 Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (UADE) is a serious adverse effect, which by its nature, incidence, severity, or outcome has not been identified, in the current version of the risk analysis report.

An anticipated serious adverse device effect (ASADE) is an effect that by its nature, incidence, severity or outcome has been identified in the risk analysis report.

6.2 Adverse Event Reporting

AE information will be collected from subject enrollment through study exit. AEs that occur during this study should be treated by established standards of care that will protect the life and safety of the subject.

The Investigator will report any AEs to the Sponsor and will assess AEs for their relationship to the device and therapy, and whether or not the event meets the definition of

serious. Subsequent intervention required, resolution status and whether or not the AE resulted in the subject's discontinuation in the study will also be reported.

Any SAE or UADE must be reported to the Sponsor within 24 hours of knowledge of the event. The Investigator is responsible for notifying the Institutional Review Board (IRB), as required by the site-specific IRB requirements.

All AEs must be recorded, as applicable, on the case report forms provided.

6.3 Device Observations and Malfunctions

A device malfunction is defined as failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use.

All device malfunctions are required to be documented on a case report form, reported to the Sponsor and, if required, reported to the IRB within the required timeframe.

In the event of a suspected device malfunction or device observation, the device and accessories will be returned to the Sponsor for analysis. Instructions for returning the device will be provided by the Sponsor.

All device malfunctions will be evaluated by Cala Health staff. Serious injuries and/or deaths during the study will be evaluated to determine if the Cala Trio device might have malfunctioned or contributed to the event.

7.0 Data Quality Assurance

7.1 Data Collection and Storage

Data will be collected using case report forms (CRFs) designed specifically for this study. The data will be analyzed by Cala Health staff and reviewed by the investigators and a biostatistician, as needed. Investigators will be responsible for completion and timely submission of the forms to Cala Health for data processing.

Cala Health quality assurance procedures are designed to ensure that complete, accurate, and timely data are submitted, that protocol requirements are followed, and that complications and adverse device effects are reported. Incoming data are reviewed to identify inconsistent or missing data and adverse effects. Data problems will be addressed in calls to the investigational site and during site visits.

Collected data will be stored on paper documents or on a 21 CFR Part 11-compliant electronic data capture (EDC) system. All paper documents will be securely stored at the study sites. Each subject's data will be de-identified by assigning a unique identification number per subject. This identification number will be assigned by the researchers at the time of consent. The identification number will be securely stored at the study site, and only researchers involved in the study will have access to the information in the cabinet.

Investigators are to maintain all source documents as required by the protocol, including worksheets and Informed Consent forms. The source documents can be used by Cala Health staff (as needed) to verify information submitted on the CRFs.

8.0 Site Training

The Sponsor, or designee, is responsible for the training of clinical site personnel, including the Investigator, sub-investigator(s), research coordinator(s), and other participating site staff. The Sponsor will conduct initial training on Cala Trio use, data collection, proper reporting of AEs, compliance with the protocol, informed consent process and associated activities necessary to conduct this clinical study in accordance with the regulations and Good Clinical Practices.

8.1 Protocol Deviations

Any deviations from the study plan identified during monitoring visits or through other means will be documented on CRFs. These include, but are not limited to items such as the following:

- Failure to obtain written informed consent prior to conducting study related measurements
- Subject enrolled that does not meet inclusion/exclusion criteria
- Subject received stimulation using the wrong device (i.e. a right-handed device was used on the left wrist or a device of the wrong size was used)

If the study site demonstrates a pattern of consistent and frequent deviations, the Sponsor will undertake appropriate activities (e.g. re-training) to attempt to bring the site into compliance with the protocol. A pattern of repeated serious deviations from the protocol may result in site termination from the study.

9.0 Statistical Methods

9.1 General Principles

Standard summary statistics will be calculated for all study variables. For continuous variables, statistics will include means, standard deviations, medians and interquartile ranges. Categorical variables will be summarized in frequency distributions.

One-sided statistical tests will have p-values less than 0.025 deemed significant while two-sided tests will have p-values less than 0.05 deemed significant. Statistical analyses will be conducted in SAS version 9.3 or above (SAS Institute, Cary, N.C.), R version 3.2 or above (R Foundation for Statistical Computing, Vienna, Austria) or another validated statistical software package.

9.2 Safety Endpoint Analysis

The safety of the Cala Trio device will be evaluated by the incidence of device and therapy-related adverse events. Additionally, all adverse events documented during study conduct will be tabulated and reported.

9.3 Primary Effectiveness Endpoints Analyses

Primary endpoint for the study is defined as within subject comparison of tremor power before stimulation to after stimulation. Statistical testing of the primary endpoint will be

based on the cohort of all enrolled and treated subjects for whom outcome data are available.

The statistical objective related to the primary endpoint is to demonstrate that Parkinson's disease action hand tremor is reduced from pre-stimulation values at baseline to post-stimulation values at 4 weeks, under treatment with the Cala Trio device. Formally, the null and alternative hypotheses to be tested for each primary endpoint are as follows:

H_0: $\mu_T \geq 0$

H_A: $\mu_T < 0$

where μ_T is the change from pre-stimulation at baseline to post-stimulation at 4 weeks in the endpoint in question.

9.4 Secondary Effectiveness Endpoint Analysis

The study secondary endpoint is defined as within subject comparison of ADLs and UPDRS across Visit 1-3 captured as defined in the protocol. Statistical analyses will be performed incorporating intra-subject correlation for repeated measures, and as for the primary endpoint the statistical objective is to demonstrate that Parkinson's disease action tremor is reduced under treatment with the Cala Trio device.

Null and alternative hypotheses are analogous to those shown above.

9.5 Additional Exploratory Effectiveness Analyses

Additional exploratory analyses include:

- Patient Session Impression of Improvement (PSI-I)
- UPDRS modified Part III (tremor tasks only) – subset relevant to non-stimulated hand
- UPDRS modified Part III (tremor tasks only) and ADL pre- versus post-stimulation within each visit
- ADLs based on recall
- Product Survey
- Device usage metrics
- CGI-S/I, PGI-S/I

Note that the same UPDRS modified Part III (tremor tasks only) are collected on the non-stimulated hand in order to determine if the device has a bilateral effect.

The listed analyses will be evaluated using analogous statistical methods as described for the primary and secondary endpoints.

9.6 Planned Analyses

All participants in this study will be using the same device as the commercial users of Cala Trio diagnosed with ET, with a common user interface workflow. As with all commercial users, an accelerometer on the device will measure tremor power before and after a subset of 40-minute therapy sessions (every session for the first 40 sessions, followed by every 7th session thereafter). Subject-reported ratings of the therapy sessions (improved, no change, worsened) will be recorded after the acceleration measurements on the device.

The analysis will evaluate de-identified data from up to 50 subjects who complete Cala Trio therapy sessions during 4 weeks of at-home use. Subjects will be given instruction on how to calibrate the device's stimulation to their hand tremor frequency and will be instructed to use the therapy twice daily at home. Therapy efficacy will be quantified using improvement in tremor power pre- and post- stimulation. Tremor severity will be visually rated for all subjects by an expert rater according to UPDRS and the ADL score will be noted.

Formal analyses of the primary and secondary endpoints will be conducted after completion of study. It will take place once 50 subjects have reached the 4-week visit, at which time analyses subgroups of interest will also be investigated, tabulated and reported.
Study hypotheses will be tested for p-values of 0.05 and 0.01.

9.7 Sample Size and Power

The study sample size (N) is predicated on primary endpoints as detailed above. Assuming same effect from the ET-14 data, at p = 0.01 we have the following results.

Metric	p value	N
Kinematic measurements for study duration of 2 weeks	0.01	40
Kinematic measurements for study duration of 4 weeks	0.01	30

Under these effect sizes, assuming up to 10% data attrition and with a paired difference test at 0.01 alpha against the null hypothesis of no change from baseline, the 34 to 50 subject analysis provides at least 90% power for simultaneous testing of the primary endpoint.

10.0 Study Administration

10.1 Institutional Review Board Approval

The study protocol will be reviewed and approved by the Investigator's IRB prior to subject enrollment. The Sponsor and the IRB prior to implementation must approve proposed significant changes to the clinical study protocol. A significant change is one which may increase the risk or present a new risk to a subject, affects the subject's rights or welfare, or which may adversely affect the scientific validity of the study.

Investigators are responsible for obtaining and maintaining annual renewal of the study by their IRB (or according to renewal schedule imposed by the IRB).

10.2 Amending the Protocol

The protocol, subject informed consent, or other clinical investigation documents shall be amended as needed throughout the clinical investigation. Proposed amendments to the protocol shall be agreed upon between the Sponsor and Investigator (or delegate). The amendments to the protocol and the subject's informed consent form shall be notified to, or

approved by, the IRB and regulatory authorities. The version number and date of amendments shall be documented.

10.3 Privacy and Confidentiality

Subject data obtained in connection with this clinical study will be treated as confidential and will be disclosed only as required by law. A number will identify subjects, not a name. The subject informed consent discloses how subject information is collected and used, and all subjects must consent in writing prior to any study-related treatments.

10.4 Record Retention

Investigators will maintain complete, accurate and current study records in accordance to the requirements in the IDE regulation (21 CFR 812).

These records shall be maintained for a period of two years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a regulatory submission.

10.5 Device Accountability

Device accountability records will be maintained at the study site. Devices used during the study will be recorded in the device accountability and disposition logs.

10.6 Sponsor Responsibilities

The Sponsor (Cala Health, Inc.) is responsible for:

- Ensuring that the study is designed and managed in compliance with all appropriate regulatory standards and is conducted according to the protocol
- Selecting qualified investigators and providing them with the information and materials necessary to conduct this study in compliance with the protocol and local applicable regulatory requirements
- Providing appropriate training to Investigators, site staff and all sponsor representatives to conduct this study in compliance with the protocol and local applicable regulatory requirements
- Securing compliance with the clinical protocol, investigator agreement, and local regulations
- Confirming that IRB review and approval are obtained prior to subject enrollment or conducting protocol-required testing
- Ensuring that the Investigators and the reviewing IRB are promptly notified of significant new information about this clinical study
- Supervising the overall conduct of the study: ensuring proper monitoring of the clinical study and data, analyzing data (including evaluations of AEs) and preparing study reports
- Controlling the distribution of the device(s) under investigation.

10.7 Investigator Responsibilities

The Investigator is responsible for the following:

- Ensuring sufficient time and resources (including qualified staff and facilities) are available to manage the day-to-day conduct of the study, and ensuring data integrity and the rights, safety and well-being of subjects
- Obtaining approval from the IRB, including subsequent protocol amendments and changes to the subject informed consent and obtaining renewals throughout the duration of the study
- Compliance with the clinical study protocol and applicable regulatory requirements
- Investigational device accountability and use of the investigational device in accordance with the approved protocol
- Reporting all SAEs to the Sponsor as soon as possible after knowledge of the event, and to the IRB as specified in the requirements.

11.0 Publication

The Sponsor may disclose the results of the study through a publication or any other public disclosure. A Publications Review Committee may be formulated to oversee the publication process. Authorship on a primary publication of the results from this study will be based on contributions to study design, enrollment, data analysis, and interpretation of results.

12.0 References

[1] Nonnekes J et al Unmasking Levodopa Resistance in Parkinson's Disease. Movement Disorders 2016.

[2] Yahr MD, Duvoisin RC, Schear MJ, Barrett RE, Hoehn MM. Treatment of parkinsonism with levodopa. Arch Neurol 1969; 21(4):343-354.

[3] Louis, E. D. (2015). More Time with Tremor: The Experience of Essential Tremor Versus Parkinson's Disease Patients. *Movement Disorders Clinical Practice*.

[4] Walsh, D. M., Howe, T. E., Johnson, M. I., Moran, F., & Sluka, K. A. (2009). Transcutaneous electrical nerve stimulation for acute pain. *The Cochrane Library*.

[5] Dubinsky, R. M., & Miyasaki, J. (2010). Assessment: Efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review) Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*, *74*(2), 173-176.

[6] Vance, C. G., Dailey, D. L., Rakel, B. A., & Sluka, K. A. (2014). Using TENS for pain control: the state of the evidence. *Pain management*, *4*(3), 197-209.

[7] Yoo, P. B., Hincapie, J. G., Hamann, J. J., Ruble, S. B., Wolf, P. D., & Grill, W. M. (2011, August). Selective control of physiological responses by temporally-patterned electrical stimulation of the canine vagus nerve. In *Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE* (pp. 3107-3110). IEEE.

[8] Birdno, M. J., Kuncel, A. M., Dorval, A. D., Turner, D. A., Gross, R. E., & Grill, W. M. (2012). Stimulus features underlying reduced tremor suppression with temporally patterned deep brain stimulation. *Journal of neurophysiology*, *107*(1), 364-383.

[9] Brocker, D. T., Swan, B. D., Turner, D. A., Gross, R. E., Tatter, S. B., Koop, M. M., ... & Grill, W. M. (2013). Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease. *Experimental neurology*, *239*, 60-67.

[10] Miocinovic, S., Khemani, P., Whiddon, R., Zeilman, P., Martinez-Ramirez, D., Okun, M. S., & Chitnis, S. (2014). Outcomes, management, and potential mechanisms of interleaving deep brain stimulation settings. *Parkinsonism & related disorders*, *20*(12), 1434-1437.

[11] Tass, P. A., Qin, L., Hauptmann, C., Dovero, S., Bezard, E., Boraud, T., & Meissner, W. G. (2012). Coordinated reset has sustained aftereffects in Parkinsonian monkeys. *Annals of neurology*, *72*(5), 816-820.

[12] Hanajima, R., Dostrovsky, J. O., Lozano, A. M., Hutchison, W. D., Davis, K. D., Chen, R., & Ashby, P. (2004). Somatosensory evoked potentials (SEPs) recorded from deep brain stimulation (DBS) electrodes in the thalamus and subthalamic nucleus (STN). *Clinical neurophysiology*, *115*(2), 424-434.

[13] Klostermann, F., Wahl, M., Schomann, J., Kupsch, A., Curio, G., & Marzinzik, F. (2009). Thalamo-cortical processing of near-threshold somatosensory stimuli in humans. *European Journal of Neuroscience*, *30*(9), 1815-1822.

[14] Brittain, J. S., Cagnan, H., Mehta, A. R., Saifee, T. A., Edwards, M. J., & Brown, P. (2015). Distinguishing the Central Drive to Tremor in Parkinson's Disease and Essential Tremor. *The Journal of Neuroscience*, *35*(2), 795-806.

[15] Cagnan, H., Brittain, J. S., Little, S., Foltynie, T., Limousin, P., Zrinzo, L., ... & Brown, P. (2013). Phase dependent modulation of tremor amplitude in essential tremor through thalamic stimulation. *Brain*, awt239.

13.0 Revision History

Protocol Version	Summary of Changes	Author
A	Initial Release	Ruta Deshpande