Protocol Title

Cranial Electrotherapy Stimulation for the Treatment of

Major Depressive Disorder in Adults (CES-MDD)

Sponsor

FISHER WALLACE LABORATORIES, INC.

630 FLUSHING AVENUE

SUITE #104

BROOKLYN, NEW YORK 11206

Protocol Number:

FW-200-05

Version Number:

5.0

Version Date:

07-Jun-2022

Confidentiality Statement

This study will be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and the Belmont Report. Study conduct will comply with applicable US FDA, state, and local Regulations.

PROTOCOL APPROVAL PAGE

Protocol Title: Cranial Electrotherapy Stimulation for the Treatment of Major Depressive Disorder in Adults (CES-MDD)

Protocol Number: FW-200-05

Date: 07-Jun-2022

We the undersigned have read and approve the clinical investigational plan specified above and agree on its content:

DocuSigned by: Kelly Roman Signer Name: Kelly Roman Signing Reason: I approve this document Signing Time: 29-Nov-2022 | 14:13 PST 7650734344D74EE98D32DD08D7E72515 Kelly Roman, CEO, Fisher Wallace Laboratories, Inc.	29-Nov-2022 | 14:13 PS Date
DocuSigned by: Dr. Kyle Lapidus, MD, PhD Signer Name: Dr. Kyle Lapidus, MD, PhD Signing Reason: I approve this document Signing Time: 29-Nov-2022 | 06:32 EST 96D894493D9647D49D110A47172488A0 Kyle Lapidus, MD, PhD, Principal Investigator	29-Nov-2022 | 06:33 EST Date

INVESTIGATOR STATEMENT OF COMPLIANCE

I have read this protocol and agree to conduct and/or supervise the study in accordance with the relevant, current protocol, in accordance with accepted good clinical practice principles, and will only make changes in a protocol after notifying Fisher Wallace Laboratories, Inc. and receiving written authorization from Fisher Wallace Laboratories, Inc.

I agree to obtaining the written and dated approval of an Institutional Review Board (IRB) prior to initiation of the study and will promptly file all required reports with the IRB.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

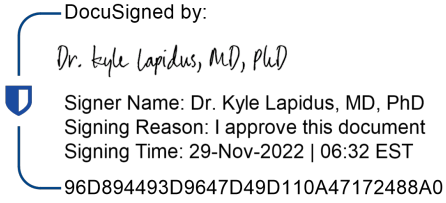
I agree to maintain adequate and accurate records and to make those records available for inspection to both Fisher Wallace Laboratories, Inc. and regulatory authorities, and to assist Fisher Wallace Laboratories in resolving any questions regarding study data

I agree to disclose to Fisher Wallace Laboratories, Inc. accurate financial information as required by FDA regulations (21 CFR 54).

I agree to maintain the confidentiality of this study, all study related documents and data; and will not disclose any content without prior written consent; provided, however, that I may submit the results of the study for publication upon giving Fisher Wallace Laboratories 30 days in which to review the manuscript for confidential information and to protect and perfect any intellectual property rights.

The signature below attests that I have read and understand the contents of this protocol (or revisions to the protocol) and will adhere to the study protocol requirements as presented including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. Federal Regulations.

Investigator Signature:



PROTOCOL REVISION HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	29-Mar-22	Not Applicable	Initial Version
2.0	19-Apr-22	Exclusion Criteria Modification	Addition of Exclusion Criteria to Exclude Employees, Family Members or Personal Associate of the Sponsor
3.0	16-May-22	Exclusion Criteria Modification	Concomitant Medication Clarification and Hospitalization Language Clarification
4.0	19-May-22	Revision to Baseline Instrument Inclusion Criteria	Participants are not excluded due to PHQ-9 & QIDS-SR baseline scores outside of moderate range
5.0	08-Jun-22	Modification to the study target population	Allow enrollment of patients with severe depression and corresponding higher baseline BDIII scores

LIST OF ABBREVIATIONS/ACRONYMS

TERM	DEFINITION
ADE	Adverse Device Effect
AE	Adverse Event
BDI-II	Beck Depression Inventory Second Edition
CDC	Centers for Disease Control and Prevention
CES	Cranial Electrotherapy Stimulation
CMOS	Complementary Metal Oxide Semiconductor
CRO	Contract Research Organization
DBS	Deep Brain Stimulation
DD	Device Deficiency
DMP	Data Management Plan
ECT	Electroconvulsive Therapy
ePRO	Electronic Patient Reported Outcomes
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
IRB	Institutional Review Board
JBI	James Blinding Index
LED	Light Emitting Diode
MDD	Major Depressive Disorder
MINI	Mini-International Neuropsychiatric Interview
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
QIDS-SR	Quick Inventory of Depressive Symptomatology Self-Report

RCT	Randomized Controlled Trial
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAFTEE	Systematic Assessment for Treatment of Emergent Events
SOP	Standard Operating Procedure
TMF	Trial Master File
TMS	Transcranial Magnetic Stimulation
UADE	Unanticipated Serious Adverse Device Effect
VNS	Vagus Nerve Stimulation

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1 GENERAL

1.1 SPONSOR INFORMATION

The sponsor of this study is:

Fisher Wallace Laboratories, Inc.

630 Flushing Avenue, Suite #104

Brooklyn New York, New York 11206

1.2 PRINCIPAL INVESTIGATOR, COORDINATING INVESTIGATORS AND INVESTIGATION SITE(S) CONTACT INFORMATION

The Principal Investigator (PI) for this study is:

Kyle Lapidus, MD, PhD

300 West 72 Street #1D New

York, NY 10023

kylelapidus@gmail.com

(917) 969-3445

1.2.1 List of Investigative Sites and Roles of Parties

The FW-200-05 trial is a decentralized clinical investigation due to the COVID-19 pandemic. As Principal Investigator, Dr. Kyle Lapidus will oversee the study conduct and the safety of the subjects. Climb will establish and maintain the electronic patient reported outcomes (ePRO)/electronic data capture platform, provide clinicians to qualify subjects for study participation, and provide investigative staff for non-clinical subject assistance including subject training on device handling. Climb will also support Fisher Wallace Laboratories, Inc. (Sponsor) with coordinating the shipping of investigational devices to subjects. NAMSA (CRO) will be responsible for supporting the Sponsor with study management activities.

1.2.2 List of External Organizations

Climb

1808 Wedemeyer St. Suite 326
San Francisco, CA 94129
(415) 484-8997

www.climb.care

NAMSA
400 Hwy 169 S, Suite 500
Minneapolis, MN 55426
(763) 287-3830
www.namsa.com

1.3 OVERVIEW OF CLINICAL INVESTIGATION

Full Title	**C**ranial **E**lectrotherapy **S**timulation for the Treatment of **M**ajor **D**epressive **D**isorder in Adults
Short Title	CES-MDD
Protocol Number	FW-200-05
Protocol Version	Version 5.0
Study Sponsor	Fisher Wallace Laboratories, LLC. 630 Flushing Avenue, Suite #104 Brooklyn New York, New York 11206
Study Purpose	This prospective, fully remote, randomized, controlled, triple-blind (subject, Principal Investigator, Sponsor) pivotal study is designed to evaluate the safety and efficacy of the Fisher Wallace Stimulator FW200 to deliver Cranial Electrotherapy Stimulation (CES) for the treatment of moderate to severe Major Depressive Disorder (MDD) in adults.
Investigational Product	Fisher Wallace Stimulator® FW-200
Study Objective	To demonstrate the safety and effectiveness of FW-200 CES selfadministered for the treatment of moderate to severe MDD in adults

Study Endpoints	**Primary:** ● Change in the Beck Depression Inventory Second Edition (BDIII) at week two compared to baseline. **Secondary:** ● Change in the BDI-II at weeks one and four compared to baseline. ● Change in the Patient Health Questionnaire-9 (PHQ-9) and Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) at weeks one, two, and four compared to baseline. ● BDI-II responder rate at four weeks. **Safety:** ● Determine the rate of device related adverse events.
Study Design	Remote, decentralized, randomized, controlled, triple blind (subject, Principal Investigator, Sponsor), pivotal investigation
Inclusion Criteria	1. Age 21-65 years and a resident of the United States of America 2. Meets DSM-5 diagnostic criteria for moderate to severe Major

	Depressive Disorder 3. Baseline BDI-II score between 20 and 63, inclusive (in Moderate to Severe range) 4. Able to receive packages to their home via UPS/Fedex/USPS or other delivery service 5. Willing and able to send and receive study related text messages on an internet capable mobile device throughout the duration of the study 6. Owns and uses a personal, verifiable email address 7. Able to commit to two (2) 20-minute treatment sessions per day for 4 weeks, one treatment upon waking for the day and one treatment before going to bed 8. Willing to abstain from use of recreational drugs, hypnotics, steroids, and/or marijuana products through study completion 9. Willingness to not initiate treatment for a mental health issue during the course of the study 10. Fluent in English 11. Sexually active females of childbearing potential willing to commit to practicing at least one or more of the following methods of contraception during the study: intrauterine device (IUD), barrier method in combination with a spermicide, oral/hormonal contraception, or abstinence 12. In the opinion of the investigator, able to comply with study requirements and complete the study

Exclusion Criteria	1. History of suicide attempt or active suicidal ideation with plan or intent in the past 30 days. 2. In the opinion of the investigator, considered high risk of suicide 3. Previous hospitalization or institutionalization for mental health condition within one year of study entry. 4. Underwent electronic brain stimulation or neuromodulation within the past one year, including CES, transcranial magnetic stimulation, electroconvulsive therapy, and deep brain stimulation 5. Modification of prescription medications that affect the nervous system including those for mental health issues within 30 days of study entry. A patient who has been on a stable dose of prescription medications that affect the nervous system or being used for a mental health issue for at least 30 days prior to study entry and are not expected to modify their medication while on the trial are allowed to participate. 6. Use of recreational drugs, hypnotics, steroids, and/or marijuana products in the past 30 days 7. History of alcohol use disorder or other substance use disorder in the past 12 months 8. Females currently pregnant or planning to conceive during study participation, or unwilling to comply with birth control requirements 9. Known history of heart disease 10. Known history of trigeminal neuralgia 11. Implanted with an electronic device such as a defibrillator, deep brain stimulator, or pacemaker 12. Unstable medical condition including any condition requiring hospitalization or change in treatment in the prior 30 days
	13. Legally blind and/or deaf and without in-home care service to assist with study participation 14. Meets M.I.N.I. assessment criteria for, or has been diagnosed with, any of the following: Bipolar I disorder, bipolar II disorder, other specified bipolar and related disorder, panic disorder, agoraphobia, social anxiety disorder (social phobia), obsessive-compulsive disorder, posttraumatic stress disorder, alcohol use disorder in the past 12 months, substance use disorder (non-alcohol) in the past 12 months, any psychotic disorder (e.g., schizophrenia, schizoaffective disorder), major depressive disorder with psychotic features, anorexia nervosa, bulimia nervosa, binge-eating disorder, generalized anxiety disorder, any cognitive or developmental disorder (e.g., autism, Down's Syndrome), any personality disorder or psychiatric disorder that may interfere with study participation 15. Current participation in another investigational study or participated in an investigational study within the past 30 days 16. In the opinion of the investigator, may not be able to comply with study requirements 17. Any employee, family member, or personal associate of the Sponsor or their designees conducting the study

Target Population/ Sample Size	Adults ages 21-65 years. A total of 250 evaluable subjects (approximately 1:1 allocation) will be included in this study. Subject will be located in the United States and have a diagnosis of moderate to severe Major Depressive Disorder.
Number of Site(s)	One investigative site in the US with subject activities conducted via a decentralized/remote method.
Study Duration	Estimated subject participation time is approximately 6 weeks: 2-week lead-in period followed by 4 weeks of treatment.
Statistical Methods	Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and ClopperPearson Exact method for categorical variables. The primary endpoint is the change in BDI-II at week 2 compared to baseline. Analysis will be based on a linear model for change, adjusted for each subject's baseline value, comparing the randomized groups.

2 INTRODUCTION

2.1 BACKGROUND

Mental health treatment was the greatest healthcare cost in the U.S. prior to the pandemic, more than cancer, heart disease, or diabetes. Mental health care costs have further increased in the past two years. According to the Centers for Disease Control and Prevention (CDC), the rate of clinical depression among US adults has more than tripled since the COVID-19 pandemic began (Czeisler et al., 2020). The U.S. is in the midst of an unprecedented mental health crisis, and the American public requires treatment options that are effective, safe, and efficiently delivered to patients. There was a large, unmet clinical need for treatment of depression before COVID-19, and there will continue to be such a need after the pandemic is brought under control.

There are significant gaps in the delivery of care to patients suffering from depression. In the U.S., the majority of patients with depression who are treated with antidepressant medication receive their prescription not from a board-certified psychiatrist, but from their primary care physician. These clinicians are usually not responsible for making psychiatric diagnoses, and do not formally monitor side effects or evaluate response (Mann, 2011). Cognitive behavioral therapy and other forms of in-person psychotherapy

are expensive and require a high level of sustained patient engagement in order to be effective. Inadequate access to mental health resources has long been an issue for many segments of the U.S. population. This reality of the U.S. mental healthcare system means that Cranial Electrotherapy Stimulation (CES), as a low risk, home-based intervention, provides a potentially clinically important benefit for treating patients with depression.

Beginning approximately twenty years ago, new, effective forms of neuromodulation became available, some of which the FDA has reviewed for clinical use, including transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS). In the case of CES, which was already commercially available with long track records of safety, a number of pilot studies and a substantial amount of anecdotal evidence supported safety and effectiveness. The development of new neuromodulatory treatments greatly increased interest in the clinical potential of all forms of neurostimulation to treat depression. Scientific and clinical interest also re-focused on older methods of therapy, such as electroconvulsive therapy (ECT), which, like CES, delivers alternating current, albeit ECT delivers an exponentially higher dose of electrical stimulation designed to cause a seizure and thus requires anesthesia to administer. The Fisher Wallace Stimulator delivers a low dose of pulsed alternating current which is comfortable and safe to self-administer and is intended to be used by the patient twice a day to treat depression.

In recent years, animal and clinical research on CES for alleviating depression has increased, and it has been found that higher frequencies can overcome the impedance of the human skull (Mindes, 2015). Neurophysiological effects have been studied using concurrent brain magnetic resonance imaging (Ghobadi-Azbari, 2020) and electroencephalography (EEG) (Merlet, 2013; Miniussi, 2012). Computational modeling (Datta, 2013 a, b; Khadka, 2020) of stimulation effects using models of electrical behavior in tissues of the head, skull and brain provides additional data suggesting that stimulation may have beneficial impact.

CES is a low-cost, non-invasive, wearable form of low intensity neural stimulation that has been used clinically for over 100 years (Mindes, 2015). This body of evidence from use of CES, and comparison with other neuromodulation methods, indicate that CES is a safe form of neural stimulation that causes minimal side effects. This large body of evidence also suggested possible benefits of regular CES for a range of neuropsychiatric indications, including depression.

The Fisher Wallace Stimulator was cleared by the FDA for the treatment of depression, anxiety and insomnia in 1990 and has been on the market for 32 years - under the brand Liss Cranial Stimulator from 1990-2007, and under the brand Fisher Wallace Stimulator from 2007 to the present. Over 100 published scientific articles analyzing the safety and effectiveness of CES are available on PubMed.gov. Uncontrolled and controlled clinical studies as well as many mechanistic studies have been performed in the US, with better quality research being generated over the past decade. These studies investigated and evaluated the effectiveness and safety of CES devices in various patient populations, as well as possible biological mechanisms of action.

2.2 STUDY RATIONALE

While the precise mechanism of action for CES is not yet known, there is substantial research and decades of use showing that CES does have physiological effects on the brain, and that those effects are consistent with CES alleviating depression. This study will leverage the opportunities and efficiencies of the telehealth environment to investigate the benefits of CES for adults with moderate to severe MDD. In doing so, the study will more accurately represent the real-world experience of patients using CES, as CES devices are typically prescribed for home use, and more psychiatric care is being provided via telemedicine.

This prospective, fully remote, randomized, controlled, triple-blind study is designed to evaluate the safety and efficacy of FW-200 self-administered Cranial Electrotherapy Stimulation (CES) in adults with moderate to severe Major Depressive Disorder (MDD).

3 INVESTIGATIONAL DEVICE

3.1 INTENDED USE

The Fisher Wallace Stimulator FW-200 is a non-invasive medical device intended to treat adult patients with moderate to severe Major Depressive Disorder (MDD). The FW-200 is a prescription device for use at home by the patient without a medical professional, though the device may also be used in a professional health care setting or extended care facility.

3.2 POPULATIONS AND INDICATIONS FOR WHICH THE INVESTIGATIONAL DEVICE IS INTENDED

The indicated use is Cranial Electrotherapy Stimulation in adults (ages 21-65 years) for 20 minutes twice daily, upon waking for the day and at bedtime, to reduce symptoms of moderate to severe MDD.

3.3 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The FW-200 is a fixed output version of the commercially available FW-100 which has variable output. Whereas the commercially available FW-100 is able to deliver output at four different Levels, 1-4, the FW200 only outputs at Level 2.

The FW-200 device consists of the following components (also refer to figures below):

- CES device controller
- Electrode receptacle with sponge
- Electrode lead wires (red and black)
- Sponges 4-pack
- Velcro headband
- Carry case
- User guide
- AA batteries

Figure 1: FW-200 CES Device

Figure 2: Headset Electrode Wires and Applicator Sponges

Figure 3: Velcro Headband **Figure 4**: FW carry case **Figure 5**: Sponges 4-pack

Figure 6 demonstrates the functional principle of the FW-200 device. The controller contains a dial for users to turn the device on and off. An LED panel on the controller displays the output level of the device and confirms the device is on. Figure 8 displays images of patients wearing and handling the FW-200 device components. The controller is connected to two sponges that are secured to the patient's head with a headband.

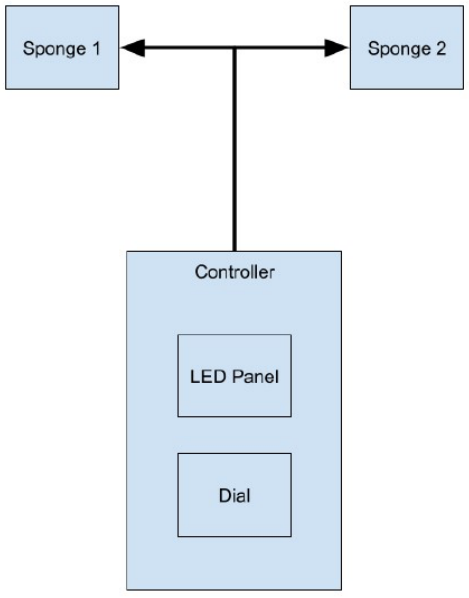

Figure 6: Functional Block Diagram

Figure 7: Wearing and Handling of the FW-200

As described in the User Guide, the patient's scalp and hair must be clean before electrode application to minimize the risk of irritation caused by placement of the electrodes. The sponge electrodes, as well as the scalp and hair beneath the electrodes, must be wet for electrode conductivity to occur. New headsets are provided with pre-installed sponges in the white plastic sponge receptacles. The sponges provided are dehydrated and will expand when wet.

After snapping the white sponge receptacles to the wires and inserting the other ends of the wires into the top of the device, patients must saturate the sponges with water. The electrode sponges should be replaced every two weeks, or if they become stained or appear degraded in any way.

The patient places the headband on the head so that it sits above the eyebrows. The wet electrodes, in the receptacles with attached wires, are placed beneath the headband, above the sideburns. The bottom of the electrode should be in line with the top of the ear. The physiological location of electrode placement is the squamous temporal bone above the very posterior part of the zygomatic arch.

Once the wet sponge electrodes are placed securely beneath the headband, with wires connected, the device is turned on by rotating the dial. The dial is rotated counterclockwise to go from the OFF to ON position (there is a click when the dial is rotated to ON). The green ON light should illuminate and the first and second (Level #2) yellow indicator lights should also flashes yellow, indicating Level #2 output. If the green ON light does not illuminate, the user should replace the batteries. If the yellow indicator lights do not illuminate, the user should press the electrodes against his/her head to expel more water, or rewet the sponges or tighten the headband.

Depending on skin sensitivity, patients may or may not feel a sensation of stimulation (prickly sensation, warmth) when the device is used on the head at Level #2. Although the dial does show four levels, all settings will administer Level #2 stimulation to the study subject.

Study subjects will use the device twice daily: once for 20 minutes after waking up for the day and once again for 20 minutes before going to bed.

3.3.1 ACCESSORIES

The FW-200 is provided as a complete kit. For any device replacement needs (lead wires, sponge receptacles, sponge pack or headband), a new complete kit will be shipped.

3.3.2 CONDITIONS OF USE

Users will be provided instructions regarding the conditions of this use. The environment where the system is used should be one that has the following operating conditions:

- Temperature range: 41 to 95°F (5 to 40°C)
- Relative humidity range: 10% to 93%, non-condensing

Do not allow water to enter the device. The Fisher Wallace Stimulator® should not be exposed to environmental conditions where the system may get wet. Operation in close proximity (e.g., within 1m) to a shortwave or microwave therapy equipment may reduce the output performance of the device.

Keep the device out of reach of children. Electronic monitoring equipment such as ECG monitors and ECG alarms may not operate properly when CES stimulation is in use. High frequency surgical equipment may not be used when CES stimulation is in use. This device is not suitable for use with oxygen or in the presence of a flammable anesthetic mixture with air or oxygen, or with nitrous oxide.

3.3.3 CLEANING THE DEVICE

The device and headset require cleaning for reuse. Reference the User Guide for the cleaning instructions. Investigative staff and subjects will be trained on the cleaning process during device handling training.

3.3.4 SIGNAL FORMS

Both the monopolar waveforms in the FW-200 will make use of three frequencies: 1) 15 kHz; 2) 15 Hz; and 3) 500 Hz. The 15 kHz frequency refers to the carrier frequency. The 500Hz frequency controls the on and off times of the carrier. The 15Hz frequency controls the polarity reversal of the combined 15kHz and 500Hz signals. The voltage amplitude of the output signal is the same for both polarities. The combined voltage amplitude will be twice the monopolar form.

3.3.5 VOLTAGE AND CURRENT OUTPUT

The FW-200 has been designed to provide a constant current. This is done with a fixed voltage and a resistive feedback circuit called the Constant Current Controller. Users should be receiving approximately 2 mA peak-to-peak (in the monopolar scheme) and 4 mA peak-to-peak (in the bipolar scheme).

Voltage and current are directly related to each other by the resistance of the load (in this case the human head). Therefore, a constant current controller was needed to address the variability in the resistance of the human head. The constant current controller adjusts its own resistance so that the human head plus the controller will produce a fixed current for the Output voltage. At a resistance of 100 Ohms, the voltage output is approximately 400 mV. At 200 Ohms, the voltage output is double, approximately 800 mV.

The average current output relates to the modulation of the signal. If the voltage was applied constantly, the average current would be 2mA because it is being modulated the average current is reduced by each duty cycle: 50% due to the 15kHz on/off carrier modulation; 50% due to the 500Hz on/off modulation of the carrier and 75% due the off time between the 15Hz polarity reversal.

That provides an average current of 0.375 mA.

3.3.6 ELECTRONICS/CONTROLLER

Figure 9 below is a block diagram of the electronics system. It demonstrates the key connections between the major systems that make up the Printed Circuit Board Assembly (PCBA). The batteries provide power for the entire system operation. The microcontroller (MCU) takes input from the Dip Switch and a Rotary switch. In turn, it controls the light emitting diodes (LEDs) and the complementary metal oxide semiconductor (CMOS) Analog Switch. The MCU will also power the LEDs to visually affirm that the device is on. The Voltage Regulator takes power from the Batteries and increases the voltage for the output circuitry. The Microcontroller produces the three frequencies and modulates the Output using the CMOS Analog Switch. The Analog Switch is able to both turn on and off the voltage as well as swap the Output's polarity. The Constant Current Controller maintains current through the Output by the use of a resistive feedback circuit. This circuit varies its own resistance so that 2mA is maintained even if there are differences at the output. The Microcontroller will drive the Buzzer to indicate the end of the session.

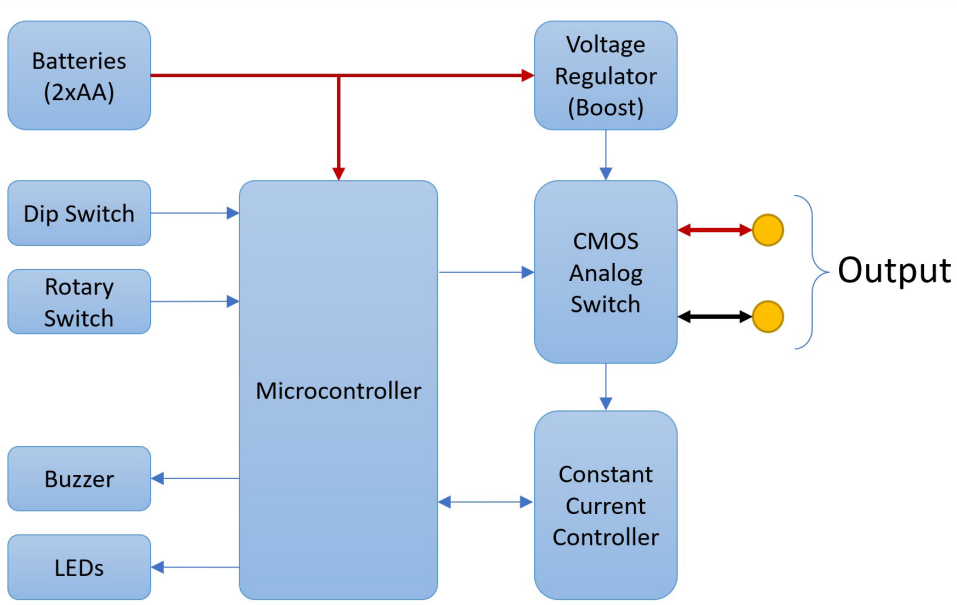

Figure 9: Electronics Block Diagram

3.3.7 SOFTWARE

The FW-200 contains firmware. All functions of the device are controlled by integrated circuits.

3.4 MANUFACTURER OF THE INVESTIGATIONAL DEVICE

The FW-200 is manufactured by Fisher Wallace Laboratories, Inc. via its contract manufacturer.

3.5 MODEL NAME AND NUMBER INCLUDING SOFTWARE VERSION AND ACCESSORIES

The names, model numbers and versions of the components of the FW-200 to be used in this study are provided in Appendix 1.

3.6 DEVICE TRACEABILITY DURING AND AFTER THE CLINICAL INVESTIGATION

The FW-200 and the accessory components are identifiable by lot number, equipment number, or serial number. These component lot numbers and reference numbers will be tracked by the Sponsor using a device accountability log. Return of investigational products will be reconciled against clinical study shipping logs.

The Sponsor or designee shall keep records documenting the receipt, use, and return of the investigational devices. Dispositions of all investigational devices will be maintained in the ePRO.

The FW-200 devices and accessories will remain within the expiry date for the duration of the clinical study. FW-200 devices and accessories will be replaced in study site inventory and returned to the Sponsor prior to their expiry date. Replacement FW-200 devices will be provided as necessary.

3.7 Device Materials in Contact with Tissues or Body Fluids

The FW-200 materials that will be in direct contact with tissues are listed Appendix 1.

3.8 Summary of Training and Experience Needed to Use the Investigational Device

The FW-200 components are intended for use at home by study subjects.

Prior to the subject receiving the study device, a member of the investigative team will verify that the subject has completed a self-paced video training detailing the device components, how to use them, and how to clean them for personal reuse. Additionally, investigational staff will conduct a live demonstration via video conference of the device including a review of the User Guide with the subject. The subject will be required to confirm his/her understanding of device usage and cleaning process prior to using the FW200 independently. The investigational team will be available to answer device-related questions upon request from a subject. Subject training completion will be documented in the ePRO.

4 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

4.1 Summary of Non-Clinical/Preclinical Studies

The following testing has been completed:

Non-Clinical Section	Description/Test Results
Electrical Safety and Electromagnetic Compatibility	Electrical safety and EMC testing demonstrated compliance with IEC 60601-2- 10:2012, AMD1:2012; IEC 60601-1:2015, AMD1:2012; IEC 60601-1-11:2015, AMD1:2012; BS EN 60601-1:2006 + A12:2014, and IEC/EN 60529:2013.
Software	Software documentation and verification and validation testing was completed for the FW-200 software, which has Moderate Level of Concern.
Sterilization and Shelf-Life	The Fisher Wallace Stimulator, Model FW-200 is not provided sterile. Accelerated shelf-life testing has been completed and has validated a 5year shelf-life for the FW-200 as of 3/8/2022. Reference report #EMTS290227 via EMTS Lab Inc. Fisher Wallace plans to conduct a realtime shelf-life study to validate a 5-year shelf life.

Bench Performance Testing	Bench performance testing was conducted as recommended in FDA's Special Controls for CES devices, including: ● Waveform ● Output mode ● Pulse duration ● Frequency ● Train delivery ● Maximum charge and energy Stress/wear testing was conducted to verify that the device thumbwheel and headband withstand use throughout the expected use life of the device. Passing results were achieved.

4.2 SUMMARY OF CLINICAL STUDIES

To examine the safety and effectiveness of the Fisher Wallace Stimulator, Model FW- 200, for treatment of major depressive disorder (MDD), a double-blind randomized controlled trial (RCT) was performed in a fully remote fashion during the COVID-19 pandemic. Subjects with either mild, moderate, or severe major depressive disorder were enrolled in the study. Throughout the treatment period, participants administered twice daily 20-minute treatments with either the active device or a sham device treatment. Participants were randomized into immediate or delayed treatment arms. In the immediate treatment arm, participants administered active treatment (20 minutes of clinical stimulation per treatment session) for 8 weeks. Participants in the delayed treatment arm received sham stimulation (two seconds of clinical stimulation and 19 minutes and 58 seconds of zero stimulation per treatment session) for 4 weeks, before being unblinded. At that point, participants were crossed over to active treatment for the following 4 weeks.

Participants completed reports of compliance with treatment, as well as assessments of symptoms and side effects throughout the study, particularly at weeks 2, 4, and 8. Physician assessments were performed prerandomization and at 4 weeks.

The primary outcome measure was change in Beck Depression Inventory Second Edition (BDI-II) score from baseline to week 4 in immediate versus delayed treatment arms. The BDI-II is a widely used selfreported instrument to assess the severity of depression in adolescents and adults from different cultural groups and populations (Beck Depression Inventory-Second Edition | The National Child Traumatic Stress

Network, n.d.). Secondary outcome measures included: change in Hamilton Depression Rating Scale from baseline to week 4, change in BDI-II from baseline to week 2, change in BDI-II from week 4 to 8, change in Patient Health Questionnaire-8 from baseline to week 2 and week 4, as well as safety and tolerability as measured by Systematic Assessment for Treatment of Emergent Events (SAFTEE).

This study enrolled 275 participants with 137 participants in the Immediate Treatment arm and 138 participants in the Delayed Treatment arm. Of these, 83 participants in the Immediate Treatment arm and 78 participants receiving delayed treatment completed 4-week assessments.

Table 1 provides the percentages of side effects experienced by subjects in both treatment arms at Week 4. Table 2 displays the percentages of patient-reported side effects at Week 8. There were no reported serious adverse events. Overall, more adverse events were reported in the Delayed Treatment arm than the Immediate Treatment arm. Minor symptoms reported were similar in both groups with 13/34 symptoms on SAFTEE reported more frequently in the Immediate Treatment group and 21/34 symptoms reported more frequently by individuals in the Delayed Treatment arm.

Table 1: Side Effects Reported by Subjects at Week 4

	Immediate Treatment	Delayed Treatment	Total
Have you felt weak?	14.0% (8/57)	15.1% (8/53)	14.5% (16/110)
Have you felt drugged or like a zombie?	3.5% (2/57)	5.7% (3/53)	4.5% (5/110)
Have you been sweating more than usual?	5.3% (3/57)	7.5% (4/53)	6.4% (7/110)
Have you felt tired during the day?	54.4% (31/57)	66.0% (35/53)	60.0% (66/110)
Have you had difficulty staying awake during the day?	22.8% (13/57)	30.2% (16/53)	26.4% (29/110)
Have you had difficulties waking up fresh in the morning?	56.1% (32/57)	62.3% (33/53)	59.1% (65/110)

Have you gained weight?	21.1% (12/57)	18.9% (10/53)	20.0% (22/110)
Do you think some foods taste different/odd?	7.0% (4/57)	11.3% (6/53)	9.1% (10/110)
Have you felt more hungry than usual?	14.0% (8/57)	17.0% (9/53)	15.5% (17/110)
Have you been more thirsty than usual?	24.6% (14/57)	22.6% (12/53)	23.6% (26/110)
Have your stools been hard or difficult to pass?	15.8% (9/57)	20.8% (11/53)	18.2% (20/110)
Have you needed to go to the toilet often?	24.6% (14/57)	17.0% (9/53)	20.9% (23/110)
Has your skin been more sensitive to the sun?	0.0% (0/57)	0.0% (0/53)	0.0% (0/110)
Have you noticed any areas of darker skin?	0.0% (0/57)	3.8% (2/53)	1.8% (2/110)
Are you experiencing any skin irritation where you place the Fisher Wallace device?	7.0% (4/57)	3.8% (2/53)	5.5% (6/110)
Do you have diabetes?	3.5% (2/57)	5.7% (3/53)	4.5% (5/110)
Have you been told that your blood sugar levels are high?	8.8% (5/57)	15.1% (8/53)	11.8% (13/110)
Have you noticed a change in your blood sugar levels?	0.0% (0/57)	0.0% (0/53)	0.0% (0/110)
Has your vision been blurry?	8.8% (5/57)	15.1% (8/53)	11.8% (13/110)
Have your eyes felt dry and gritty?	15.8% (9/57)	24.5% (13/53)	20.0% (22/110)

Are you experiencing any unusual eyestrain or headaches?	22.8% (13/57)	17.0% (9/53)	20.0% (22/110)
Have you found that your words dont come out clearly?	7.0% (4/57)	3.8% (2/53)	5.5% (6/110)
Have you found it difficult to swallow?	1.8% (1/57)	1.9% (1/53)	1.8% (2/110)
Have you felt anxious?	49.1% (28/57)	34.0% (18/53)	41.8% (46/110)
Have you felt agitated?	33.3% (19/57)	26.4% (14/53)	30.0% (33/110)
Have you lost interest in enjoyable things?	42.1% (24/57)	34.0% (18/53)	38.2% (42/110)
Have you experienced fits/jerks?	1.8% (1/57)	1.9% (1/53)	1.8% (2/110)
Have your arms or legs been shaky?	3.5% (2/57)	11.3% (6/53)	7.3% (8/110)
Have you had restless legs?	8.8% (5/57)	22.6% (12/53)	15.5% (17/110)
Have you been less interested in sex?	17.5% (10/57)	24.5% (13/53)	20.9% (23/110)
Have you found it difficult to enjoy sex?	15.8% (9/57)	13.2% (7/53)	14.5% (16/110)
Have you been unable to reach orgasm?	24.6% (14/57)	18.9% (10/53)	21.8% (24/110)
Have the areas around your nipple been sore and/or swollen?	3.5% (2/57)	0.0% (0/53)	1.8% (2/110)
Have you experienced any side effect at all including but not limited to those you've already answered?	19.3% (11/57)	7.5% (4/53)	13.6% (15/110)

Each row of the table includes only those subjects with a response of Yes or No.

Table 2: Side Effects Reported by Subjects at Week 8

	Immediate Treatment	Delayed Treatment	Total
Have you felt weak?	18.0% (11/61)	11.7% (7/60)	14.9% (18/121)
Have you felt drugged or like a zombie?	8.2% (5/61)	3.3% (2/60)	5.8% (7/121)
Have you been sweating more than usual?	6.6% (4/61)	10.0% (6/60)	8.3% (10/121)
Have you felt tired during the day?	63.9% (39/61)	63.3% (38/60)	63.6% (77/121)
Have you had difficulty staying awake during the day?	21.3% (13/61)	28.3% (17/60)	24.8% (30/121)
Have you had difficulties waking up fresh in the morning?	65.6% (40/61)	61.7% (37/60)	63.6% (77/121)
Have you gained weight?	26.2% (16/61)	20.0% (12/60)	23.1% (28/121)
Do you think some foods taste different/odd?	0.0% (0/61)	15.0% (9/60)	7.4% (9/121)
Have you felt more hungry than usual?	18.0% (11/61)	13.3% (8/60)	15.7% (19/121)

Have you been more thirsty than usual?	18.0% (11/61)	20.0% (12/60)	19.0% (23/121)
Have your stools been hard or difficult to pass?	26.2% (16/61)	25.0% (15/60)	25.6% (31/121)
Have you needed to go to the toilet often?	18.0% (11/61)	10.0% (6/60)	14.0% (17/121)
Has your skin been more sensitive to the sun?	0.0% (0/61)	3.3% (2/60)	1.7% (2/121)
Have you noticed any areas of darker skin?	3.3% (2/61)	5.0% (3/60)	4.1% (5/121)
Are you experiencing any skin irritation where you place the Fisher Wallace device?	4.9% (3/61)	1.7% (1/60)	3.3% (4/121)
Do you have diabetes?	1.6% (1/61)	6.7% (4/60)	4.1% (5/121)
Have you been told that your blood sugar levels are high?	6.6% (4/61)	3.3% (2/60)	5.0% (6/121)
Have you noticed a change in your blood sugar levels?	1.6% (1/61)	0.0% (0/60)	0.8% (1/121)
Has your vision been blurry?	13.1% (8/61)	18.3% (11/60)	15.7% (19/121)
Have your eyes felt dry and gritty?	26.2% (16/61)	20.0% (12/60)	23.1% (28/121)
Are you experiencing any unusual eyestrain or headaches?	16.4% (10/61)	21.7% (13/60)	19.0% (23/121)

Have you found that your words dont come out clearly?	8.2% (5/61)	5.0% (3/60)	6.6% (8/121)
Have you found it difficult to swallow?	0.0% (0/61)	1.7% (1/60)	0.8% (1/121)
Have you felt anxious?	37.7% (23/61)	33.3% (20/60)	35.5% (43/121)
Have you felt agitated?	29.5% (18/61)	26.7% (16/60)	28.1% (34/121)
Have you lost interest in enjoyable things?	37.7% (23/61)	31.7% (19/60)	34.7% (42/121)
Have you experienced fits/jerks?	3.3% (2/61)	1.7% (1/60)	2.5% (3/121)
Have your arms or legs been shaky?	1.6% (1/61)	1.7% (1/60)	1.7% (2/121)
Have you had restless legs?	8.2% (5/61)	11.7% (7/60)	9.9% (12/121)
Have you been less interested in sex?	19.7% (12/61)	21.7% (13/60)	20.7% (25/121)
Have you found it difficult to enjoy sex?	14.8% (9/61)	13.3% (8/60)	14.0% (17/121)
Have you been unable to reach orgasm?	9.8% (6/61)	15.0% (9/60)	12.4% (15/121)
Have the areas around your nipple been sore and/or swollen?	0.0% (0/61)	3.3% (2/60)	1.7% (2/121)
Have you experienced any side effect at all including but not limited to those you've already answered?	18.0% (11/61)	8.3% (5/60)	13.2% (16/121)
Each row of the table includes only those subjects with a response of Yes or No.			

Subjects in the Immediate Treatment arm experienced a decrease of 10.4 points in BDI-II scores. This decrease of greater than ten points is indicative of antidepressant effectiveness.

More than 40% of the patients had a decrease of 50% in BDI-II or more. Due to high levels of placebo response, the between group difference in BDI-II change was -0.8 ($p = 0.496$). Significantly, and despite the fairly large drop in BDI-II during the first four weeks in the sham arm, the switch to active treatment was associated with additional improvement (BDI-II decrease from week 4 to 8 of 3.6 points) beyond what they had experienced during the first four weeks, while the Immediate Treatment arm only showed minimal additional improvement in this period (BDI-II decrease of 0.6 points, $p < 0.01$), representing an improvement of more than 15% from BDI-II scores from the end of the sham period. Thus, the data demonstrate the effectiveness of the FW-200 in treating depression.

5 BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE AND CLINICAL INVESTIGATION

5.1 ANTICIPATED CLINICAL BENEFIT

Participation in this study may treat moderate to severe Major Depressive Disorder in adults (ages 21-65).

Knowledge gained from this study may enable future patients to benefit from CES.

5.2 POTENTIAL ANTICIPATED ADVERSE EVENTS

Potential anticipated adverse events are those that may occur in association with a CES treatment, including those AEs listed below that are known risks from clinical experience/use of the FW-200 and similar CES devices (*Federal Register :: Neurological Devices; Reclassification of Cranial Electrotherapy Stimulator Devices Intended To Treat Anxiety and/or Insomnia; Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator Devices Intended To Treat Depression*, n.d.).

Risks associated with CES and CES devices include:

- Skin irritation
- Headaches
- Dizziness
- Electrical shocks and burns

The FW-200 is contraindicated for patients with the following:

- Demand or sensing type pacemakers, or any other form of implanted electronics
- Known heart disease
- A poor reaction to the idea of electrical stimulation of any kind
- Skin irritation around either electrode site
- The device should not be used around the Carotid sinus

As stated in the CES-MDD User Guide section, the FW-200 should not be used on the throat, neck or eyes. Subjects should avoid using the device near areas of the body where there is embedded shrapnel or metal plates. There is no danger to subjects using the device who have had dental fillings.

Subjects may experience skin irritation at the site of sponge electrode placement, especially if the sponges deteriorate or if contact is made between the skin and the metal part of the sponge receptacle, or if the sponges are not thoroughly wet before each use. Please refer to the CES-MDD User Guide for more information.

5.3 Steps to Control or Mitigate the Risks

A Risk Management Program has been established by Fisher Wallace Laboratories. Risks associated with the FW-200 have been minimized by the design, labeling, and or training. An experienced investigator and site staff as well as licensed psychiatric care providers have been chosen to conduct this study. They have been trained on the study protocol as well as the investigational device. They are familiar with the disease state, moderate to severe MDD, and have appropriate experience to evaluate and navigate changing care needs for the subjects, if applicable. Adverse events will also be monitored throughout the study by the Principal Investigator and/or designee using the ePRO.

5.4 Residual Risks Associated with the Investigational Device

Residual risk is defined as the risk remaining after protective measures have been taken. The residual risk was reviewed by the Sponsor and deemed acceptable or acceptable with continuous monitoring.

5.5 Other Complications and Risks in Clinical Use

There are no additional risks or complications known during clinical use beyond those already listed in this protocol.

5.6 Risk-to-Benefit Rationale

It is expected that subjects enrolled in this study will not be exposed to risks beyond those normally associated with CES devices. CES devices have been extensively studied and the risks have been shown to be low. There was a low rate of adverse events in prior research with the FW-200.

The FW-200 may reduce the risk of moderate to severe MDD in adults. A prior study of the FW-200 in adults with mild, moderate, and severe MDD demonstrated very low risk of the device itself, in addition to a trend towards improvement in MDD symptoms by week 2 of device usage.

Based upon review of the risk measures taken with the device and the results of prior studies with the FW200, as well as the risk mitigation measures in the protocol, and consideration of the potential benefits to study subjects or future patients, the risk/benefit profile for the FW-200 is considered acceptable and justifies conducting this study.

6 OBJECTIVES AND HYPOTHESIS OF THE CLINICAL INVESTIGATION

6.1 RATIONALE FOR STUDY ENDPOINTS SELECTION AND MEASUREMENT

The primary endpoint is the change in the Beck Depression Inventory Second Edition (BDI-II) at week two of study therapy compared to baseline. A two-week time point for the primary endpoint offers the ability to detect an acute change in patient status with use of the FW-200, which may be an advantage over other therapies. For example, pharmacological treatment can require titration to a full therapeutic dose, which may depend on individual patient characteristics, including the patient's age, treatment setting, comorbidities, concomitant pharmacotherapy, or specific medication side effects, all which may lead to a lengthy titration process. Psychotherapy approaches require a similar tailored approach. Guidelines note that for both pharmacological and psychotherapy approaches may require 4 to 8 weeks of treatment (Gelenberg, 2010).

Secondary endpoints include: Change in BDI-II scores at one and four weeks compared to baseline, change in PHQ-9 and QIDS-SR scores at one week, two weeks, and four weeks compared to baseline, and BDI-II responder rate (i.e., % of subjects with a 50% or better improvement in score from baseline) at four weeks. The PHQ-9 is a validated tool for assessing depression severity and response to treatment (Nida, n.d.) The QIDS-SR has been demonstrated to be a valid measure of depression symptom severity in both research and clinical settings (Rush et al., 2003). The secondary endpoints of BDI-II at one and four weeks plus the BDIII responder rate at four weeks aim to provide additional evidence of effectiveness over additional time points.

Safety of the FW-200 will be assessed with standard adverse event data collection over the course of the study, comparing sham-assigned subject data to active treatment subject data. Adverse events for both sham and active device subjects will be MedDRA coded and analyzed for trends.

During this trial, the subject, Principal Investigator, and Sponsor will be blind to the study treatment assignment. The James Blinding Index will be used to assess blinding after the subject completes training on device usage.

Only subjects with moderate to severe MDD will be enrolled in the trial. This triple blind, sham controlled study intends to collect data to demonstrate that the FW-200 device delivers CES that improves symptoms of moderate to severe MDD in adults.

6.2 PRIMARY OBJECTIVE

To demonstrate the safety and effectiveness of FW-200 CES self-administered for the treatment of moderate to severe MDD in adults.

6.2.1 PRIMARY ENDPOINT

This study's primary endpoint is the change in BDI-II score at two weeks compared to baseline.

6.3 SECONDARY ENDPOINTS

This study's secondary endpoints include:

- Change in BDI-II score at one and four weeks compared to baseline.
- Change in PHQ-9 and QIDS-SR scores at one week, two weeks, and four weeks compared to baseline.
- BDI-II responder rate (i.e., % of subjects with a 50% or better improvement in score from baseline) at four weeks

6.4 SAFETY ENDPOINTS

The safety endpoint is to determine the rate of device and procedure related adverse events.

6.5 OBSERVATIONAL DATA COLLECTION

An evaluation of subject James Blinding Index (JBI) responses versus treatment allocation after initial device training will be performed.

7 DESIGN OF THE CLINICAL INVESTIGATIONS

7.1 GENERAL

This prospective, fully remote, randomized, controlled, triple-blind (subject, Principal Investigator, Sponsor) pivotal study is designed to evaluate the safety and efficacy of the Fisher Wallace Stimulator FW-200 to deliver Cranial Electrotherapy Stimulation (CES), self-administered, for the treatment of moderate to severe Major Depressive Disorder (MDD) in adults over 4 weeks.

7.1.1 Study Procedures and Evaluations

Potential subjects will complete an online pre-screening process to assess whether they are potentially qualified to participate in this study. Pre-screening questions will include inclusion/exclusion criteria, demographics, medical history, and concomitant medications. Candidate subjects will also take the BDI-II and PHQ-9 assessments. Select questions from the Mini International Neuropsychiatric Interview (M.I.N.I.) will also be required. The ePRO will be programmed to determine if the candidate's answers meet eligibility criteria for the study. If not, the candidate will be notified via email or SMS text that they are not suitable for study participation. If the candidate meets pre-screening eligibility, the ePRO will notify the candidate via email or SMS text that a member of the investigational staff will be in contact to further discuss study requirements and eligibility.

Investigative staff will speak with pre-screened potential subjects by telephone to describe study expectations and perform the informed consent process. Investigative staff will also ask the candidate to confirm that data provided during the pre-screening process is accurate and is allowed to be used for study evaluation purposes. If the candidate subject does not consent to study participation or the use of their prescreening data, the candidate will be deemed a pre-screen failure. If the candidate subject signs the

informed consent form and allows the use of their pre-screening data, the candidate will advance to study enrollment.

From the point of enrollment, subjects in screening will begin a 14-day minimum lead-in period. At the conclusion of the lead-in period, screened subjects will retake the BDI-II and PHQ-9 assessments, and additionally take the QIDS-SR assessment to establish baseline data. A BDI-II score between 20 and 63, inclusive, will serve to indicate that a subject's moderate to severe MDD has been stable during the lead-in period.

If the BDI-II score is not within the range, the subject's MDD will be considered insufficiently stable for study entry. The subject will be notified that they are no longer eligible for study participation and they will be considered a screen failure.

If the screened subject's data is within the acceptable range for the BDI-II, the subject will advance to scheduling a meeting with a clinician from the investigative team. Via teleconference, the clinician will administer the M.I.N.I. assessment and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) evaluation.

If the clinician identifies that the subject's results do not meet both M.I.N.I. and DSM-5 criteria for moderate to severe MDD, the subject will be notified that they are no longer eligible for study participation. Additionally, during the live interview, the clinician may deem the subject a screen failure should they no longer meet all inclusion criteria or meet any exclusion criteria.

If the clinician diagnoses the subject with moderate to severe MDD based on the results of the M.I.N.I. and DSM-5 assessments, and determines that the subject meets all other eligibility criteria, the subject will be prescribed study treatment by the clinician and be randomized to a study treatment arm (sham device or active treatment device). Only eligible subjects will be enrolled in the study, randomized to a treatment arm, and receive an investigational device shipped directly to them by an unblinded Sponsor designee.

Prior to starting self-administered therapy with the FW-200 sham or active device, subjects will review an online device training video and undergo a live device and ePRO training with investigative staff. The day after successfully completing live training with investigative staff, subjects will begin self-administered therapy twice per day, one 20-minute session after waking for the day and one 20-minute session before going to bed. Each day of study therapy, subjects will confirm in ePRO that they completed both treatment sessions for the day. Subjects will also be asked if there have been any changes to their medications or health status within the past 24 hours. This will be captured as free text to allow subjects to describe any positive or negative (adverse events) experiences during study therapy.

At the following time points, subjects will retake the BDI-II, PHQ-9, and QIDS-SR assessments:

- Week 1 (Day 7 of therapy)
- Week 2 (Day 14 of therapy)
- Week 4 (Day 28 of therapy)

For the Week 1 and Week 2 evaluations, subjects will have 2 additional days to complete the assessments. For the Week 4 evaluation, subjects will have 5 additional days to complete the assessments. Should a

subject complete one of these assessments outside the allowed time window, this instance will be documented as a minor protocol deviation. Subjects will not be withdrawn from the study for minor protocol deviations.

Subject participation in the study concludes after completion of the Week 4 evaluation. At that time, subjects will be contacted to return the investigational device and log in ePRO any adverse experiences or medication changes within the past 24 hours.

7.1.2 Measures to Minimize or Avoid Bias

The Principal Investigator is an expert user of the study device and will serve as a trainer on device handling for investigative staff. All investigative staff will be trained on the use of the device, this protocol, use of the ePRO, and Good Clinical Practices (GCP). Additional training may be provided to the Principal Investigator or investigative staff by Climb, NAMSA, or the Sponsor as needed.

This study is prospective, randomized, sham controlled study, triple blinded for the subject, Principal Investigator, and Sponsor. Randomization provides a level of protection against bias as it tends to balance all confounders, both measured and unmeasured. Pre-specified endpoints and analysis plans, with a statistically powered sample size further minimize the potential for bias. The planned two-week lead-in period to establish a stable baseline should minimize bias due to regression to the mean.

7.2 SUBJECTS

7.2.1 Inclusion Criteria for Subject Selection

Subjects will need to meet all the following inclusion criteria:

1. Age 21-65 years and a resident of the United States of America
2. Meets DSM-5 diagnostic criteria for moderate to severe Major Depressive Disorder
3. Baseline BDI-II score between 20 and 63, inclusive (in moderate to severe range)
4. Able to receive packages to their home via UPS/FedEx/USPS or other delivery service
5. Willing and able to send and receive study related text messages on an internet capable mobile device throughout the duration of the study
6. Owns and uses a personal, verifiable email address
7. Able to commit to two (2) 20-minute treatment sessions per day for 4 weeks, one treatment upon waking for the day and one treatment before going to bed
8. Willing to abstain from use of recreational drugs, hypnotics, steroids, and/or marijuana products through study completion
9. Willingness to not initiate treatment for a mental health issue during the course of the study 10.

   Fluent in English

11. Sexually active females of childbearing potential willing to commit to practicing at least one or more of the following methods of contraception during the study: intrauterine device (IUD), barrier method in combination with a spermicide, oral/hormonal contraception, or abstinence
12. In the opinion of the investigator, able to comply with study requirements and complete the study

7.2.2 Exclusion Criteria for Subject Selection

Subjects will not meet any of the following exclusion criteria:

1. History of suicide attempt or active suicidal ideation with plan or intent in the past 30 days
2. In the opinion of the investigator, considered high risk of suicide
3. Previous hospitalization or institutionalization for mental health condition within one year of study entry
4. Underwent electronic brain stimulation or neuromodulation within the past one year, including CES, transcranial magnetic stimulation, electroconvulsive therapy, and deep brain stimulation
5. Modification of prescription medications that affect the nervous system including those for mental health issues within 30 days of study entry. A patient who has been on a stable dose of prescription medications that affect the nervous system or being used for a mental health issue for at least 30 days prior to study entry and are not expected to modify their medication while on the trial are allowed to participate.
6. Use of recreational drugs, hypnotics, steroids, and/or marijuana products in the past 30 days
7. History of alcohol use disorder or other substance use disorder in the past 12 months
8. Females currently pregnant or planning to conceive during study participation, or unwilling to comply with birth control requirements
9. Known history of heart disease
10. Known history of trigeminal neuralgia
11. Implanted with an electronic device such as a defibrillator, deep brain stimulator, or pacemaker
12. Unstable medical condition defined as any condition requiring hospitalization or change in treatment in the prior 30 days
13. Legally blind and/or deaf and without in-home care service to assist with study participation
14. Meets M.I.N.I. assessment criteria for, or has been diagnosed with, any of the following: Bipolar I disorder, bipolar II disorder, other specified bipolar and related disorder, panic disorder, agoraphobia, social anxiety disorder (social phobia), obsessive-compulsive disorder, posttraumatic stress disorder, alcohol use disorder in the past 12 months, substance use disorder (non-alcohol) in the past 12

months, any psychotic disorder (e.g., schizophrenia, schizoaffective disorder), major depressive disorder with psychotic features, anorexia nervosa, bulimia nervosa, binge-eating disorder, generalized anxiety disorder, any cognitive or developmental disorder (e.g., autism, Down's Syndrome), any personality disorder or psychiatric disorder that may interfere with study participation

15. Current participation in another investigational study or participated in an investigational study within the past 30 days
16. In the opinion of the investigator, may not be able to comply with study requirements and complete the study
17. Any employee, family member, or personal associate of the Sponsor or their designees conducting the study

7.2.3 Point of Enrollment

A subject is considered enrolled in this study after they have signed the informed consent form and consented to allow the use of their data collected during the pre-screening process for study evaluations.

If either of these conditions are not met, the subject will be considered a screen failure if the ICF has been signed, or a pre-screen failure if the ICF has not yet been signed.

7.2.4 Total Expected Duration of the Clinical Investigation

The total duration of the study enrollment period is anticipated to be three months.

7.2.5 Number of Subjects Required in the Clinical Investigation

A total of 250 evaluable subjects (in a 1:1 allocation ratio of treatment and control) are initially planned for this study. The subjects will be recruited through the use of digital advertising that Climb and its affiliates will singularly manage.

7.2.6 Expected Duration of Subject Participation

The expected duration of subject participation is approximately 6 weeks. There is a 2 week lead-in process followed by 4 weeks of study treatment.

7.3 STUDY VISITS

7.3.1 Schedule of Assessments

Assessments and Device Activities	**Recruitment**		**Enrolment**					**Period 1**	**Period 1 Eval**	**Period 2**	**Period 2 Eval**	**Period 3**	**EOT**	**Unscheduled**
Activity	**Pre-Screening**	**Consent and Eligibility**[c]	**Screening Lead-In Start**	**Screening Lead-In Complete / Baseline**	**Clinical Interview / Reevaluation**[c]	**Diagnosis / Randomization**	**Subject Training**[c]	**Week 1 Device Usage**	**Week 1 Eval**	**Week 2 Device Usage**	**Week 2 Eval**	**Weeks 3-4 Device Usage**	**Week 4 Eval**	**Safety / Unscheduled**
Timeline / Window (Days)	Prior to Informed Consent	After Initial Pre-Screen and **before** Lead-In	Start of Lead-In, Minimum 14 Days before baseline	Minimum 14 Days to complete Lead-In	Prior to Day 0	Prior to Day 0	Prior to Day 0	Day 0 +7 [first day of use and continuing for 7 days][d]	Day 7 + 2 days	Days 814	Day 14 + 2 days	Day 15 – 28	Day 28 +5 days	N/A
Inclusion / Exclusion criteria[a]	X		X											
Demographics	X		X											
Beck Depression Inventory-II (BDI-II)	X		X	X					X		X		X	X

Personal Health Questionnaire Depression Scale (PHQ-9)	X		X	X					X		X		X	X
Mini-International Neuropsychiatric Interview	X		X		X[e]									
(MINI) questions														
Concomitant Medications	X		X								X		X	
Medical History	X		X											
Informed Consent		X												
Eligibility Evaluation[b]		X			X									
Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)				X					X		X		X	X

DSM-5 Interview					X									
DSM-5 Diagnosis						X								
Randomization						X								
Device Training							X							

Device Usage/Diary								X		X		X		
Device Return													X	X (if applicable)
Adverse Events								X	X	X	X	X	X	X

[a] Inclusion/Exclusion Criteria during Pre-Screening within the Recruitment Phase includes the potential subject's ability to meet inclusion or exclusion criteria that do not require assessment by a clinician from the investigative staff.

[b] Eligibility Evaluation occurs after informed consent is signed. This includes review of all potential subject data received to determine if inclusion criteria are met and no exclusion criteria are met. [c] Study Activity that requires telephone contact with the candidate subject/subject. [d] Day 0 is defined as the first day of the subject's self-administered treatment. [e] Complete M.I.N.I. interview conducted by the clinician with the subject.

7.3.2 Prescreening

Potential subjects will be directed to a website (https://trials.climb.care/participate). The website will provide potential subjects with information regarding the study and expectations. They will also be presented with an information privacy policy which they must confirm they agree with prior to submitting responses for investigative staff review.

Interested participants will complete the following pre-screening assessments in ePRO:

- Eligibility questions pertaining to Inclusion/Exclusion criteria (includes medical history and concomitant medications)
- Demographics
- BDI-II
- PHQ-9
- Questions from M.I.N.I.

The website will inform the potential subject if they are a potential candidate for the study based on their initial answers.

7.3.2.1 Demographics

The candidate subject will provide the following demographic information: self-identified gender, biological sex, age, race, and ethnicity.

7.3.2.2 BDI-II

To assess severity of depression, the potential subject will answer this 21-question multiple-choice selfreport inventory. The candidate subject's BDI-II score must be within the range of 20-63 indicating moderate to severe MDD.

7.3.2.3 PHQ-9

The candidate subject will answer this questionnaire, a 9-item scale covering the DSM criteria for major depressive disorder, with a diagnostic algorithm and score based assessment of presence and severity of depression.

7.3.2.4 Mini International Neuropsychiatric Interview (M.I.N.I.)

The candidate subject will self-report their answers to select questions from the M.I.N.I using ePRO. The M.I.N.I. is an assessment tool for the major psychiatric disorders in DSM-5 (Sheehan et al., 2010). If any answers indicate that the subject may be experiencing a condition that meets any exclusion criteria, the candidate will not advance further in the pre-screening process.

7.3.3 Consent and Initial Eligibility

Potential subjects who successfully complete the automated pre-screening process will be contacted by investigative staff to schedule a telephone or video conference. During this meeting, the investigative staff will review the purpose of the study, the daily requirements of study participation, answer any preliminary questions from the candidate, and confirm that the data provided during pre-screening is still accurate. Should the subject indicate that data reported during pre-screening requires revision/correction, the investigative staff will review the change(s) and determine if the candidate is still potentially eligible for study entry. If not, the investigative staff will inform the candidate that they are no longer able to be considered for the study. If the change does not cause the candidate to fail pre-screening, the investigative staff will make the change in ePRO and enter a reason for change in ePRO as well. The ePRO includes an audit history to display changes to reported data, the author of the change, and the date/time when the change was saved.

If the candidate agrees to learn more about the study, the study staff member will perform the informed consent process. Investigative staff will also ask the candidate to confirm that the data collected during the pre-screening process can be used for study screening and evaluation purposes. If the candidate subject does not consent to study participation or to the use of their pre-screening data, the candidate will be deemed a pre-screen failure. All pre-screening data for that candidate will not be saved in ePRO for the study. If the candidate subject signs the informed consent form and allows the use of their pre-screening data for the study, the candidate will advance to study enrollment.

7.3.3.1 **Informed Consent**

The investigative team will introduce the potential participant to the clinical investigation by explaining the protocol including the study objectives, procedures, and participation requirements.

If the potential participant is interested in participating, the study staff will review the informed consent form. This will include describing the clinical investigation, potential discomforts, risks, and benefits of participation. The potential subject will have sufficient time to decide whether they wish to participate in this clinical investigation.

Any queries that the potential participant may have regarding this clinical investigation will be addressed appropriately by the investigative team. Potential subjects will be instructed that they are free to obtain further information from the Principal Investigator and investigative team at any time and that they are free to withdraw their consent and to discontinue their participation in the clinical investigation at any time without prejudice.

If the potential participant is willing to participate in the clinical investigation, he/she must read, understand and sign the informed consent form. The informed consent form will be sent to the potential subject electronically via a validated signature program such as DocuSign. The potential subject will be asked to complete the electronic signature of the form. The Principal Investigator or designee who conducted the informed consent discussion will also sign. A copy of the signed consent will be provided to the subject electronically.

Written or electronic informed consent from the subject must be obtained before any clinical investigation related procedures are performed.

7.3.4 Screening Lead-In and Baseline

Upon signing the informed consent form, subjects will begin the screening lead-in period of 14-days minimum. No data will be collected from the subject during this time; however, the data collected during pre-screening will be saved in ePRO as study eligibility data.

After 14 days of lead-in time, subjects will be prompted to retake the BDI-II and PHQ-9 assessments in ePRO. Subjects will also take a QIDS-SR assessment in ePRO. A subject must have a BDI-II score between 20 and 63, indicating moderate to severe MDD, at both initial pre-screening and baseline to participate in the study.

If the BDI-II assessment score is not within the moderate to severe MDD range, the subject's health will be considered insufficiently stable for study entry. The subject will be notified that they are no longer eligible for study participation and they will be considered a screen failure.

If the screened subject's data is within the moderate to severe MDD range for the BDI-II assessment, the subject will advance to scheduling a meeting with a clinician from the investigative team.

7.3.5 Clinical Interview and Eligibility Reevaluation

Subjects with baseline BDI-II scores within the range of moderate to severe MDD will be contacted to schedule a meeting with a clinician from the investigative staff.

During this teleconference or video conference with the subject, the clinician will conduct the M.I.N.I. and DSM-5 assessments to evaluate the subject for moderate to severe MDD. If the clinician determines that the subject cannot be diagnosed with moderate to severe MDD, the subject will be deemed a screen failure and discontinued from study participation. Subjects who have or appear to have any of the following diagnoses or conditions will also be excluded from further study participation and documented as a screen failure:

- Bipolar I disorder
- Bipolar II disorder
- Other specified bipolar and related disorder
- Panic disorder
- Agoraphobia
- Social anxiety disorder (social phobia)
- Obsessive-compulsive disorder
- Posttraumatic stress disorder
- Alcohol use disorder in the past 12 months
- Substance use disorder (non-alcohol) in the past 12 months
- Any psychotic disorder (e.g., schizophrenia, schizoaffective disorder)
- Major depressive disorder with psychotic features
- Anorexia nervosa

- Bulimia nervosa
- Binge-eating disorder
- Generalized anxiety disorder
- Any cognitive or developmental disorder (e.g., autism, Down's Syndrome)
- Any personality disorder or psychiatric disorder that may interfere with study participation

Subjects who meet moderate to severe MDD criteria per the M.I.N.I. and DSM-5 assessment will be diagnosed as having moderate to severe MDD by the clinician.

After confirming a diagnosis of moderate to severe MDD for the subject, the clinician will review the subject's reported information in ePRO to ensure the subject continues to meet study eligibility criteria. Any subject who fails to fulfill any element of the inclusion and exclusion criteria will be considered a screen failure.

Subjects who meet all study eligibility criteria and receive a diagnosis of moderate to severe MDD from the clinician will advance to receiving a prescription for an investigational device to be used during the study.

7.3.6 Subject Identification and Randomization

Once eligibility is confirmed by the clinician and a prescription is written for the investigational device, the subject will be assigned a unique identification (ID) number by Climb. The subject ID number will consist of 01 for the first subject, 02 for the second subject, and so on. This number will be used to identify the subject during their participation in the study. Climb will maintain a log of all subjects enrolled in the clinical study including their names, their study ID number, and contact information.

The subject will also be randomized (approximately 1:1) to either the treatment group (active device) or the control (sham device). Climb will create and maintain the randomization table and assign subjects to each group. The randomization data will be restricted to unblinded investigative staff members only until the conclusion of the study. The unblinded team will be responsible for maintaining the randomization table.

7.3.6.1 **Device Shipment**

An unblinded investigative staff member who is not associated with any other function of the study will receive the subject's randomization allocation and contact/shipping address information. The study device type, either sham or active treatment, assigned to the subject through the randomization process will be directly shipped to the location requested by the subject by a third party vendor in collaboration with the unblinded investigative staff member.

7.3.7 Subject Training

The subject will be advised to not use the investigational device until after receiving live training. Prior to the live training, the subject will be asked to complete online device training using pre-recorded videos.

Once the subject receives the investigational device, they must participate in a live training with investigative staff to further learn how to correctly place and use the device, clean the device components that will be reused, and complete data collection in ePRO. The trainer will explain that the device is locked

at Level 2 and that the subject may or may not feel a sensation of stimulation, regardless of whether the device is a placebo or active device.

The subject will confirm in ePRO that their training was completed. The trainer will also record in ePRO that training was completed. The subject will continue to have access to the pre-recorded instructional video and usage manual during the study as needed for additional reference and may contact the investigative staff for device handling support during the study.

7.3.7.1 **James Blinding Index**

After participating in the live device training session with investigative staff, the subject will be asked in ePRO which type of investigational device they believe they received (active device or control). The subject will select from 5 options to indicate if they strongly believe they have an active device, somewhat believe they have an active device, do not know, somewhat believe they have a sham device, or strongly believe they have a sham device. The subject's response will be analyzed using the James Blinding Index.

7.3.8 Period 1: Week 1 Device Usage

Subjects will begin using the investigational device the day after the live training session with investigative staff. Subject will use the device as instructed, for 20 minutes after waking for the day and for 20 minutes prior to going to bed. Each day of study therapy, subjects will report in ePRO whether or not they used the study device as instructed and if there had been a change to their health status or medications over the previous 24 hours.

7.3.9 Period 1: Week 1 Evaluation

After completion of at least 1 week (7 days plus up to 2 additional days) of device usage, subjects will be requested to complete the following in ePRO:

- BDI-II
- PHQ-9
- QIDS-SR
- Any Adverse Events
- Any changes to their reported concomitant medications

7.3.10 Period 2: Week 2 Device Usage

Subjects will continue daily use of the device and report in ePRO whether or not they used the study device as instructed and if there had been a change to their health status or medications over the previous 24 hours.

7.3.11 Period 2: Week 2 Evaluation

After completing Week 2 (7 days plus up to 2 additional days) of device usage, subjects will be requested to complete the following in ePRO:

- BDI-II
- PHQ-9
- QIDS-SR
- Any Adverse Events
- Any changes to their reported concomitant medications

7.3.12 Period 3: Weeks 3-4 Device Usage

Subjects will continue daily use of the device and report in ePRO whether or not they used the study device as instructed and if there had been a change to their health status or medications over the previous 24 hours.

7.3.13 End of Therapy: Week 4 Evaluation

After completion of at least 4 weeks (28 days plus up to 5 additional days) of device usage, subjects will be requested to detail or answer the following in ePRO:

- BDI-II
- PHQ-9
- QIDS-SR
- Any Adverse Events
- Any changes to their reported concomitant medications

At End of Therapy, subjects will be contacted to return the study device to the unblinded Sponsor representative. Investigative staff will verify all subject data has been completed and exit the subject from the study.

7.3.14 Unscheduled Visits

Should a subject be withdrawn early from the study, investigative staff will ask the subject to report the adverse event in ePRO (if applicable), and complete the following assessments:

- BDI-II
- PHQ-9
- QIDS-SR

The investigative staff will also assist the subject in returning the investigational device.

7.3.15 Criteria and Procedures for Subject Withdrawal or Discontinuation

7.3.15.1 Subject Withdrawal and Discontinuation

During the course of this clinical investigation, subjects will be or may elect to withdraw from further treatment.

All subjects discontinued from the clinical investigation due to an unexpected adverse device effect, directly related to the clinical investigation, will be followed by investigative staff to the best of their ability until the effect resolves, or reaches a stable condition, in case of the undesirable event of an occurred permanent impairment. Investigative staff will document in ePRO the date and reason(s) for subject withdrawal. All subjects who discontinue treatment for any reason shall be contacted by investigative staff in an effort to follow the subject for safety.

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the study personnel or institution. If a subject decides to withdraw, all study evaluations and procedures will be stopped, and an inquiry will be made about the cause of withdrawal. Climb will account for and document all subjects enrolled in the study, including those withdrawn from the study or lost to follow-up. If a subject withdraws from the clinical investigation, the reason(s) shall be reported in ePRO.

Reasons for withdrawal include, but are not limited to:

- Subject's rescission of consent.
- Any unexpected adverse device effect which is, in the opinion of the Principal Investigator, related to the device and will endanger the wellbeing of the subject if the treatment is continued.
- The development of any undercurrent illness(es), infection or condition(s) that might interfere with the Clinical Investigation Plan.
- Any problem deemed by the Principal Investigator and Sponsor to be sufficient to cause discontinuation.
- Lost to follow-up
- Death

Additional study data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent. Data collected up to the point of subject withdrawal will be used for analysis.

Subjects who are withdrawn will not be replaced if they have received the investigational device. If possible, any assessments planned for the subject on withdrawal from the clinical investigation, including adverse event collection, should be performed when intention to withdraw the subject is announced.

Subjects who are withdrawn prior to receiving an investigational device will be replaced, including screen failures.

7.3.15.2 SUBJECT REPLACEMENT

Subjects may be replaced if they are screen failures.

7.3.15.3 LOST TO FOLLOW-UP

The effort to obtain follow-up information should include 3 attempts to make contact with the subject via telephone or text. All contact efforts to obtain follow-up information should be documented in ePRO.

7.4 MONITORING

All source data and documentation will be reviewed for completeness and appropriateness by investigative staff.

The Principal Investigator and Climb will permit the Sponsor (or designee) and the FDA to inspect source documentation and data for this study. These inspections are for the purpose of verifying adherence to the protocol and the completeness and accuracy of the data recorded in ePRO.

7.4.1 Source Data and Documentation

For this patient-reported decentralized clinical trial, source data is defined as all information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. Data entered into ePRO by subjects and/or investigative staff will be considered one form of source data for this study.

Source documents are defined as printed, optical, or electronic documents containing source data, e.g., prescriptions for the device, device accountability records, and any medical records kept by the investigative staff in support of this clinical investigation.

7.4.2 Audits and Inspections

The FDA and the Notified Body have the right to conduct an audit of the clinical investigation to ensure that the clinical investigations was, in fact, performed by the investigative staff and that the data reported in support of a marketing application accurately reflects the data in the records. The authority may also inspect such studies to verify that the clinical investigation was conducted in accordance with national regulations relating to the IRB and informed consent. It is the joint responsibility of the Sponsor and the Principal Investigator to ensure that the clinical investigation has been conducted in line with all national and local regulations.

In the event that the FDA or Notified Body desires to inspect this clinical investigation, the Sponsor, Principal Investigator, Climb, and NAMSA will permit authorized inspectors to inspect all facilities and records relating to the clinical investigation and aid the Inspector to perform the audit in a timely fashion.

Separately, during the conduct of this clinical investigation, Fisher Wallace may appoint Quality Assurance (QA) personnel to audit the administration and conduct of the clinical investigation.

8 STATISTICAL DESIGN AND ANALYSIS

Statistical analysis for the study will focus on the randomized comparison of groups for study endpoints. Key elements of the planned statistical analysis are outlined below. Additional details, including more

details regarding plans for analysis populations, subgroups, secondary endpoints, handling missing data, and sensitivity analyses will be provided in a separate standalone Statistical Analysis Plan.

8.1 Analysis Population

The primary analysis will be based on intent-to-treat, with subjects analyzed as randomized regardless of treatment actually received.

8.2 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables.

8.3 Analytical Procedures

The primary endpoint is the change in BDI-II at week 2 compared to baseline. Analysis will be based on a linear model for change, adjusted for each subject's baseline value. The mathematical statement of the null and alternative hypothesis for primary endpoint is:

$$H_o: B2 \leq 0$$

Ha: B2 > 0 where B2 represents the regression coefficient from the linear model corresponding to study arm, parameterized so a regression coefficient greater than zero represents a greater mean change for the treatment group compared to the control group. The general form of the linear model for each endpoint is:

$$\Delta Y = B0 + B1Y0\ B2*X$$

where ΔY is the change in outcome from baseline at week 2, B0 is the intercept term, B1 is the coefficient for the subject's baseline value Y0, and X is the treatment group indicator (1 = treatment, 0 = sham). Multiple imputation will be employed to address missing data.

Study success will be based on successful rejection of the null hypothesis for the primary endpoint.

Subgroup analysis will be provided based on sex and race as well as potentially other baseline factors, including baseline BDI-II score.

8.4 Significance Level and Power of the Primary Endpoint and Overall Statistical Testing Strategy

The primary endpoint analysis will be performed at the one-sided 0.025 alpha level. Any other p-values and confidence intervals will be based on a nominal two-sided 0.05 alpha level (or equivalently a one-sided 0.025 alpha level as appropriate) without adjustment for multiple comparisons.

8.5 SAMPLE SIZE CALCULATION AND JUSTIFICATION

A total of 250 evaluable subjects (in a 1:1 allocation ratio) will provide 80% power assuming a population mean difference between groups of 3.2 and a common standard deviation of 9 based on a two-sided twosample t-test with an alpha of 0.05. Previous data suggests the standard deviation for 2 week improvement to be approximately 6.5; however, a conservative estimate of 9 was used for these calculations. If the observed standard deviation is less than 9, a smaller effect size will provide 80% power. In addition, this calculation is conservative since the planned test adjusting for baseline is expected to provide additional power. Sample size calculations were performed using PASS 2021 (NCSS, LLC). While some amount of missing data is expected, the primary analysis will be based on the randomized cohort of subjects and will employ multiple imputation to mitigate the impact of missing data.

The sample size for the study is practically constrained by regulatory requirements for timely submission and the impact of the COVID-19 pandemic. Accordingly, while the final formal analysis is planned for the final planned sample size, circumstances may dictate initial regulatory submission based on data available with supplemental updates provided later based on the final data set. Since the formal analysis will be based on the final planned sample size, there are no alpha implications.

9 DATA MANAGEMENT

9.1 PROCEDURES FOR DATA MANAGEMENT

Climb will be responsible for study data management according to a project plan developed for this study in collaboration with the Sponsor and designee(s).

The details of data review and querying will be described in a Data Management Plan (DMP) that will be maintained by Climb, the Principal Investigator, and the Sponsor. This plan may be updated throughout the investigation as amended data management requirements and investigation-specific data conventions are determined.

9.1.1 Electronic Patient Reported Outcomes

The Climb web-based ePRO digital health technology will be used to record and manage study data. Subjects who have been screened for study participation and signed an Informed Consent Form will selfreport their experiences during the trial using the ePRO. Subject training on ePRO usage will be conducted prior to starting study treatment with the investigational device. Investigative staff will be available to answer questions from subjects about ePRO usage and assist them with technological issues or clarifications.

Investigative staff will review all subject-entered ePRO data to monitor subject safety and identify any issues pertaining to study design or the investigational product. A subject may contact the investigative team should they wish for their reported data to be reised or corrected. An investigative team member will make the change in ePRO and enter a reason for change in ePRO as well. The ePRO includes an audit history to display changes to reported data.

9.1.2 Data Queries

Sponsor representatives reviewing subject ePRO data may contact the subject for clarification of data or to follow up for missing data. All changes to ePRO data will be captured in an audit trail.

9.1.3 Confidentiality

This clinical investigation will comply with HIPAA and any additional requirements imposed by national law concerning data protection.

A study code identification number will be used to facilitate creation of de-identified reports. Subject personal data will be processed at all times in accordance with applicable legal requirements and will be used solely for the purposes of conducting this clinical study and to aid future scientific research in the treatment of moderate to severe depressive disorder. In general, only the Sponsor or authorized designees will have direct access to subject personal data. It may also happen that representatives of national or international public health authorities (e.g., Competent Authorities) are granted direct access to subject personal data, if required by applicable law.

9.2 Procedures For Verification And Validation Of EPRO System

The ePRO used for this trial was verified and validated by Climb's procedures for data capture validation and verification.

9.3 Procedures For Data Retention

The Climb procedures for study data retention will be followed. All information in the ePRO will be stored in a secure validated database.

9.4 Specified Retention Period

The Sponsor shall maintain the records of the study during this investigation and for a period of 2 years after the later 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 premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, or a premarket notification submission.

9.5 Clinical Quality Assurance

The study will be conducted and monitored by the Sponsor and authorized designees. The Sponsor may appoint a Quality Assurance (QA) auditor to review the records and conduct of the study.

10 AMENDMENTS TO THE PROTOCOL

Any modifications to the protocol require Sponsor approval. Once completed, the revised protocol needs to be submitted to the IRB. The protocol must receive written approval as an Amendment prior to implementing the modifications.

11 DEVIATIONS FROM THE PROTOCOL

11.1 Investigator Deviations from Protocol

Major deviations from this protocol, except in emergency situations, require prior approval by the Sponsor. This provision does not apply to those changes made to reduce discomfort or overt risks to the subject. All major deviations and any procedures or actions taken by investigative staff must be documented in the ePRO and reported to the Sponsor within 2 days.

Minor deviations (e.g. assessment unable to be completed or outside visit window) may occur from time to time. The investigative staff should make their best effort to minimize such occurrences. Should a minor deviation occur, it should be documented in the ePRO in a timely manner.

11.2 Procedures for Deviation Recording, Reporting and Analyzing

All deviations will be documented in the subject's ePRO Case Report Form and reported to the Sponsor within 2 days.

11.3 Corrective and preventive actions and principal investigator disqualification criteria

Protocol deviations will be reviewed during monitoring visits. As appropriate, investigators will be required to identify corrective and preventive actions to prevent further deviations. An investigator may be disqualified from the study for repeated and/or egregious protocol deviations.

12 DEVICE ACCOUNTABILITY

12.1 Investigational Device Disposition

Access to investigational devices shall be controlled by the Sponsor and authorized designee. The investigational devices shall be used only in this clinical investigation and according to the clinical trial protocol. The Sponsor shall keep records of the type and number of all investigational devices shipped to subjects including device return or disposal.

12.2 Clinical Supplies Accountability

The investigational devices provided for use in this study are intended for use only in the clinical trial outlined in this protocol and will be used only in subjects appropriately consented in this trial. The use of the supplies for other clinical or preclinical situations is strictly prohibited. The use of the investigational supplies by any third party, outside of the provisions stated in this protocol, without the express written permission of Sponsor, is strictly prohibited. The possession and use of the supplies by subjects must be closely controlled and monitored. Subjects will be required to return the used devices at the conclusion of their study participation (End of Therapy or early withdrawal/termination). All investigational supplies that are not used on a subject will be returned to the Sponsor at the end of the study.

The Sponsor or authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

- the date of receipt,
- identification of each investigational device (lot number/serial number or unique code),
- the expiry date, if applicable,
- the date or dates of use,
- subject identification,
- date on which the investigational device was returned/removed from subject, if applicable, and,
- the date of return to the Sponsor of unused, expired or malfunctioning investigational devices, if applicable.

12.3 Investigational Device Accountability Record

Investigational devices will be shipped directly to subjects by the Sponsor's authorized blinded designee. Upon receipt of the investigational device, the subject will record confirmation of receipt in ePRO. The Sponsor's authorized designee will review ePRO device accountability data in a timely manner to ensure accurate record keeping of final disposition of all investigational materials. Device accountability data in ePRO will be reconciled with the Sponsor's investigational device shipping and return records during the trial.

13 REGULATORY COMPLIANCE

13.1 Statements Of Compliance

- This clinical investigation will be conducted in compliance with the principles that have their origin in the latest version of the Declaration of Helsinki, October 2013.
- This clinical investigation will comply with 21 CFR Parts 11, 50, 54, 56, and 812 requirements of FDA, the requirements of the IRB, ISO 14155:2020, and other applicable regional or national regulations, whichever provides the greater protection of the individual.
- This clinical investigation will not begin until required approval(s)/favorable opinion(s) have been obtained from the applicable IRB or regulatory authority.
- Any additional requirements imposed by an IRB or regulatory authority will be followed in the conduct of this clinical trial.
- The Sponsor has obtained clinical trial insurance that will cover expenses in the event of any physical injury resulting from research procedures.

13.2 Institutional Review Board

Prior to the initiation of this clinical investigation, on behalf of the Principal Investigator, Climb will submit the protocol, patient-facing materials, informed consent form template, and any other required documents to the IRB for review and approval. The Principal Investigator, and any other member of the investigative team, if a member of the IRB, must not participate in the decision-making. A list of the members of the IRB reviewing this protocol will be requested.

A signed and dated letter from the IRB granting approval/favorable opinion must be received prior to the initiation of the clinical investigation.

13.3 Provision Of Investigational Device

Investigational products will not be shipped to the first enrolled subject until investigative staff responsible for conducting device training with subjects have themselves completed the required training on device usage/handling and this clinical study protocol.

13.4 Principal Investigator's Study Reporting Responsibilities

The Investigator agrees to the following reporting responsibilities:

- Collaborate with the Sponsor, NAMSA, and Climb to provide the required reports to the IRB for the duration of the study. Copies of IRB correspondence must be provided to the Sponsor for Trial Master File filing.
- Collaborate with Climb and NAMSA to submit the Investigator's Final Report to the IRB per the IRB's requirements after the study's completion or termination.
- Collaborate with the Sponsor, Climb, NAMSA, and investigative staff to receive any pertinent details that may impact the conduct of the clinical study and require IRB reporting per IRB policy.

14 INFORMED CONSENT PROCESS

14.1 General Informed Consent Process

The Sponsor will provide a template informed consent form (ICF) for IRB review/approval.

The Principal Investigator or investigative staff designee must administer this approved ICF to each prospective study subject, and obtain the subject's signature along with the date of consent prior to enrollment in the study. The ICF for this study will be electronic and signatures will be obtained via DocuSign or a similar platform. The ICF must be obtained in accordance with the applicable guidelines of the Declaration of Helsinki, or local regulations and laws, whichever represents the greater protection of the individual. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and also be informed that withdrawal from the study will not jeopardize their future medical care. A

copy of their signed ICF must be given electronically to each subject enrolled in the study. This will be provided electronically for their records. The institutional standard subject consent form does not replace the study ICF.

15 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

In this trial, all adverse events (AEs) and device deficiencies that occur will be reported by the subject using ePRO and reviewed by the Sponsor (or designee) and Principal Investigator in a timely manner. All AEs will be followed by the Sponsor and Principal Investigator or designee until the last event has resolved, the condition has stabilized, or the subject exits the trial, whichever comes last. All follow up reports for AEs will be documented in detail in the ePRO.

15.1 DEFINITIONS

Adverse Event (AE): 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 and whether anticipated or unanticipated.

1. This definition includes events related to the investigational medical device.
2. This definition includes events related to the procedures involved.
3. For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE): Adverse Event related to the use of an investigational medical device.

1. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

2. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.

Serious Adverse Device Effect (SADE): Adverse Device Effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE): Adverse Event that led to any of the following:

(a) death;

(b) serious deterioration in the health of the subject, that resulted in any of the following:

i. a life-threatening illness or injury, or

ii. permanent impairment of a body structure or a body function including chronic diseases, or iii. inpatient or prolonged hospitalization, or

iv. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

(c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any lifethreatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

NOTE: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.

15.2 REPORTING

15.2.1 Investigator Responsibilities

All Serious Adverse Events (SAEs), Serious Adverse Device Effects (SADEs, both Anticipated or Unanticipated), including any Device Deficiency that could have led to an SADE, must be reported to the Sponsor or designee within 24 hours of knowledge of the event. It is the responsibility of the Sponsor or designee to report the occurrence of any SAE, SADE, and/or UADE to the IRB according to IRB guidelines and national laws and regulations.

The Principal Investigator or designee will contact all subjects who record an adverse event or potential adverse event in ePRO. The subject will be asked to provide the following for the event:

- Any further details about the event or the subject's experience using the investigational product not already recorded in ePRO, if deemed necessary by the investigator ● Outcome, with options to include:
  - Ongoing/Not Resolved/Not Recovered
  - Recovering/Resolving
  - Recovered/Resolved

  - ○ Recovered/Resolved with Sequelae
  - ○ Unknown
- Resolution date if the outcome is reported as recovered/resolved, with or without sequelae ● Any treatments taken for the event and/or any actions taken to receive or schedule treatment ● Action taken with the study treatment in response to the event, with options including: ○ No action
  - ○ Discontinuation of study treatment
  - ○ Temporary halt of the study treatment; if temporary halt, the subject will be asked if the event resolved or continued after stopping the study treatment and the dates when treatment was paused.
- Relationship of the event to the use of the investigational device, reported as either Related or Not related

The investigator will review all of the reported information from the subject and separately record their causality using the following options:

- Not Related: An AE which cannot be attributed to the study device.
- Unknown Relationship: The relationship of the AE to the device cannot be determined.
- Possible: The AE occurs within a reasonable time sequence to study device usage and there is some evidence to "possibly" suggest a causal relationship. However, the influence of other factors such as underlying disease, concomitant medications, or concurrent treatment may have contributed to the event.
- Probable: The temporal sequence between the device use and the event is such that the relationship is likely or subject's condition or concomitant therapy could have caused the AE.
- Definite: The AE occurs in a plausible time relationship to study device usage and cannot be explained by any concurrent disease or other devices, drugs or chemicals.

Additionally, the investigator will record in ePRO if the AE meets the definition of a Serious Adverse Event (SAE) as per the definition in Section 15.1.

15.2.2 Sponsor Responsibilities

All adverse events and device deficiencies will be reviewed by the Sponsor to assess regulatory reporting responsibilities for the event. The Sponsor will maintain records concerning adverse device effects, whether anticipated or unanticipated.

The Sponsor will immediately conduct an evaluation of any unanticipated adverse device effects (UADEs). If it is determined that a UADE presents an unreasonable risk to subjects, the Sponsor will terminate the study or the parts of the study presenting that risk as soon as possible. The results of a UADE investigation will be reported to FDA and to the IRB within 10 working days after the Sponsor first receives notice of the effect. Thereafter, the Sponsor will submit such additional reports concerning the effect as requested by FDA.

15.3 Anticipated Potential Adverse Events

Anticipated potential adverse events (AEs) consist of those related to the investigational medical device or the procedures involved in using the device, as well as AEs that occur in this study's patient population who may be receiving treatment for comorbidities. Anticipated potential AEs that may be encountered in the conduct of this study including potential AEs related to the use of the FW-200 are listed in Section 5.2 *Potential Anticipated Adverse Events*. It is possible that there are additional risks that have not been foreseen.

15.4 Emergency Contact Details

In case of an immediately reportable adverse event (UADE), contact the Sponsor:

Gordon Levites, Quality Assurance Manager

1-631-813-8612 gordon@fisherwallace.com

16 VULNERABLE POPULATIONS

ISO 14155:2020 defines a vulnerable subject as an individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Individuals who suffer from Major Depressive Disorder would be considered a vulnerable population and therefore included within this clinical investigation.

These vulnerable subjects according to the ISO 14155 definition will be asked to provide their informed consent if they are capable of providing it themselves and the consent process will be performed without undue delay. Informed consent processes shall be conducted according to national law and IRB procedures.

The protection of the rights and welfare of study participants will be overseen by the responsible IRB and the Principal Investigator.

17 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

17.1 Criteria For Suspension OR Premature Termination

The clinical study may be stopped at any time at the Sponsor's discretion.

In addition, further recruitment in the study may be stopped due to insufficient compliance with the protocol, GCP-related issues, and/or other applicable regulatory requirements, procedure-related problems, lack of enrollment, or if the number of subject discontinuations for administrative reasons is deemed too high.

17.2 Subject Follow-Up In The Case Of Study Termination

In the event of early study termination, all subjects will be contacted via telephone by the Sponsor or designee. A record of contact(s) with each subject will be maintained in the ePRO.

18 PUBLICATION POLICY

Publication policy will be addressed in the Principal Investigator clinical trial agreement.

18.1 Clinical Trial Registration

This study will be registered on www.clinicaltrials.gov per federal regulations. This study is required by the FDA to be registered in the US government database for the registration of clinical trials. Information that can be viewed by all who access the website will only include the study design, the clinicians interacting with subjects in the study, and the study results at the completion of the study. No personal information and no protected health information (PHI) will be entered into the database.

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20 APPENDICES

20.1 Appendix 1: Device Component Names, Model Numbers and Versions

The FW-200 CES Device consists of the following components:

Component	**Part/Model Number**
CES device controller	DR-9001
Electrode receptacle with sponge	DR-9010
Electrode lead wires - Red	DR-9009
Electrode lead wires - Black	DR-9008

Headband	DR-9005
Sponge pack (4 sponges)	DR-9010
Velcro headbands	DR-9005
Carry case	DR-9011
User guide	PL 1002