ProofPilot

Neurostimulation & Depression Study

Protocol Summary Document for ProofPilot Remote Studies

ProofPilot Study ID:2518

Principal Investigator

Dr. Kyle Lapidus

Study Purpose

Examine the safety and effectiveness of the Fisher Wallace Cranial Electrotherapy Stimulator Device on Major Depressive Disorder using two 20-minute per day treatment sessions over eight weeks.

Study Design

This is a fully remote trial where participants engage at home in the study using the ProofPilot study platform. All potential participant enrollment data, including proof of identity via government ID will be reviewed by licensed medical professionals in the participant's state prior to their full enrollment.

Participants will be randomized into an immediate or delayed treatment arm. The immediate treatment arm participants will be shipped an active Fisher Wallace device limited to Level 2 output even if a participant raises the dial beyond that. The participant will remain with the active device for the full 8 weeks.

In the delayed treatment arm, the participants will receive a sham device that looks exactly the same, but only provides treatment for 2 seconds. At week 4, sham arm participants will be unblinded and shipped an active device (limited to Level 2 output even if a participant raises the dial beyond that). The delayed arm participants will continue with active devices for the remaining 4 weeks of the trial.

Physicians, via a telemedicine visit, will diagnose participants, prescribe the device and provide medical oversight. Participants will self-report adherence and any adverse events on a daily basis through diaries. Self-report outcomes will be collected via online assessments at baseline, 2-week point, 4-week point and 8 week points. In addition, physicians will also conduct an assessment at baseline and week 4.

Weeks 1-4 of this protocol are intended to provide sufficient evidence of safety and effectiveness to support the FDA Premarket approval submission for the Fisher Wallace CES device. Data collected in weeks 5-8 of this protocol, relevant to an ongoing evaluation of safety and effectiveness, may be submitted to FDA in the form of an update report, in accordance with 21 CFR § 814.20(b)(13)(e).

Treatment Instructions

After receiving a prescription via remote asynchronous telemedicine, the patient is randomized to either an immediate or delayed treatment arm, and delivery of the Fisher Wallace device will be made by UPS/Fedex/UPS. Upon delivery (as identified by shipment tracking code), individuals will be presented with video how-to instructions, and treatment overviews (along with some device usage troubleshooting facts). The device packaging will also include instructions. A PDF version of the instructions, along with FAQs will be made available via ProofPilot for quick reference.

Participants will be directed to use the device twice per day for 20 minutes, once soon after waking up, and the second time per day 20 minutes prior to attempting sleep.

The study timeline will commence upon completion of the first treatment as identified by the participant in ProofPilot.

Participants who have questions about the device will be referred to ProofPilot customer support. All queries will be logged and reported at the end of the study. ProofPilot will refer those questions that can not be answered with an automated frequently asked questions system to PI Dr. Kyle Lapidus and/or the manufacturer (Fisher Wallace) for follow-up.

Primary Outcome Measures:

- Change in Beck Depression Inventory Score in "Treatment week 4" versus Baseline in immediate versus delayed arm.

Secondary Outcome Measures:

- Change in Hamilton Depression Rating Scale from Baseline to "Treatment week 4" in immediate versus delayed arm.
- Change in Beck Depression Inventory Score in "Treatment week 2" versus Baseline in immediate versus delayed arm.
- Change in Patient Health Questionnaire - 8 (PHQ-8) score at "Treatment week 4" versus Baseline in immediate versus delayed treatment arm.
- Change in Patient Health Questionnaire - 8 (PHQ-8) score at "Treatment week 2" versus Baseline in immediate versus delayed treatment arm
- Change in Beck Depression Inventory Score from "Treatment Week 4" to "Treatment week 8" in delayed treatment arm (once they have started use of the actual device).
- Device safety, tolerability and adherence over 8 week period as measured by SAFTEE

Sample Size:

Sample size for the study is based on the primary outcome measure of PHQ-8. The difference between the randomized treatment control subjects for the change in score from "Treatment Week 4" versus baseline will be compared with a two-sample t-test at the one-sided 0.025 alpha level. For a planned sample size of 175 total subjects with 1:1 allocation, the study will provide 80% power for an effect size of 0.426 where effect size is based on the ratio of the difference of means over the standard deviation.

p value: two-sample t-test at the one-sided 0.025 alpha level

Statistical Analyses:

Primary analyses of primary and secondary outcome measures will be based on the comparison of the randomized groups via t-tests for means for the change from baseline. Sensitivity analyses for the assumption of normality and for the impact of missing data will be performed. Subgroups results based on sex and race will be provided.

Inclusion/Exclusion

- Age greater than or equal to 21
- US resident
- Can receive packages to their home via UPS/Fedex/USPS
- Major Depressive Disorder
- PHQ-8 Score greater than 10 (show some signs of mild to moderate depression)
- PHQ-8 Score less than 20 (given remote study serious depressed should be excluded)
- Read/write English
- have not contemplated suicide in the past year
- not been institutionalized for mental health issues.
- not currently experiencing problems with alcohol or drug abuse
- can commit to not drinking alcohol 4 hours before bedtime for the duration of the study
- can commit to two (2) 20 minute sessions per day for 8 weeks
- has not used a brain stimulation treatment in one year
- no suspected or known history of heart disease
- no pacemaker
- not under medical supervision for other serious medical condition
- not taking opioids
- are a resident of states in which we have licensed medical professionals
- Any co occurring significant psychiatric disorder that would impair participant's particationion.
- any use of illicit drugs

Those with a PHQ-8 score greater than 20 will be directed to contact local mental health assistance and will be provided with the National Suicide Prevention Hotline number for immediate assistance.

Recruitment

Individuals in the study will be recruited in two forms targeted to the states in which we have contracted with licensed medical professionals.

- Fisher Wallace email marketing to patients who have not purchased a Fisher Wallace device and to providers who may refer patients to the study
- Digital advertising on GoodRx, Facebook, Instagram, Google and other common advertising platforms
- Physician referrals.

All potentially interested participants will be directed to the ProofPilot study recruitment page for registration and screening to begin the study.

Study Design/Methods

All participants upon expressing interest, will be asked to create an account on ProofPilot, and answer some basic demographic questions. (Birthdate, location, sex, timezone, preferred language).

All study activities, except those with the Fisher Wallace device itself, will be completed on ProofPilot. ProofPilot is available across any internet connected device with a reasonable screen size. No download is required.

At enrollment, the participant will be asked a series of screening questions, will complete the PHQ-8, the Beck Depression Inventory and a self administered version of the MINI.

Eligible individuals who will be self consented online, will then be asked to take a photograph with their mobile device of a government issued ID for identification. Participants will set an appointment on ProofPilot with a licensed telemedicine psychiatrist in their state within the next several days.

At that virtual visit, the physician will review the participant's responses to the MINI, and add several additional elements that require a physician assessment. Then the physician will administer the HAM-D - and make a final determination if the participant is a good for the study and authorize a prescription for the device.

Participants will then complete additional baseline measures including the QIDS-SR, PROMIS Sleep Disturbance, and Jenkins Sleep Scale. They will then enter in shipping information to place an order for the Fisher Wallace Device.

All participants will be randomized, with a 50/50 chance, into a control arm or active treatment arm. Control arm participants will receive an active treatment device at the end of week 4. This is a double blind design, the participants, nor any study staff, except those conducting fulfillment are aware of which arm the participant is in until unblinding at the end of the study.

Eligible individuals will then be asked to take a photograph with their mobile device of a government issued ID for identification. They will then enter in shipping information to place an order for the Fisher Wallace Device.

Participants will then complete additional baseline measures including the QIDS-SR, PROMIS Sleep Disturbance, and Jenkins Sleep Scale.

Meanwhile, collected data from PHQ-8, and the Beck Depression Inventory along with proof of identification will be reviewed by medical oversight licensed in the state in which the participant resides and the order released with a prescription for the device. An appointment will be made for the physician to meet with the patient over video telemedicine. During this visit, the physician will evaluate the patient using previously collected baseline data, and their own assessments (MINI, HAM-D) to ensure proper diagnosis and set a professional assessment baseline.

Should the physician feel the participant is a good match, they will issue the prescription for the Fisher Wallace device.

Shipments will be fulfilled by the sponsor's fulfillment capacity by individuals who are not affiliated with the study. All study staff, including remote physicians, will be blinded to who receives the sham and who receives the active device. Tracking information from UPS/Fedex/USPS will trigger tasks based on where the shipment is in the fulfillment process, including at delivery.

At delivery, ProofPilot will automatically trigger instruction tasks, a treatment expectancy survey, and a notification to "Start the trial." The "Start the trial" task will trigger the 2 week, 4 week and 8 week follow up points key to the outcome measures. It will also trigger the window period for the final (week 4) participant/physician video teleconference assessment.

Participants will receive a daily treatment diary at 6:45AM (though they may complete it anytime within an 18 hour period). The daily treatment diary will ask about treatment adherence and any adverse events from the prior day and provide a morning treatment reminder. Participants will also receive an evening

treatment reminder at 7:15PM. Reminders will be presented from ProofPilot in the morning and in the evening adjusted for the participant timezone.

At the end of the study, participants will need to return both the active and sham devices to qualify for compensation.

At the 2 week, 4 week and 8 week (unless otherwise noted) time point from "Start of Trial" participants will repeat baseline measures:

- **PHQ-8**: Covers the DSM-IV criteria for major depressive disorder with a discriminant validity of .89 to .92[1] [2]
- **Beck Depression Inventory:** 21-question multiple-choice self-report inventory, one of the most widely used psychometric tests for measuring the severity of depression.
- **MINI: T**he M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training. The MINI is used in a participan self-administered format, and will be reviewed during a telemedicine visit with a licensed physician to help diagnose major depressive disorder and rule out other mental health disorders.
- **Hamilton Rating Scale for Depression (HAM-D)** (at baseline and 4 week point only)**:** Used by physicians to rate the severity of participant's depression symptoms.
- **QIDS-SR (Quick Inventory of Depression Symptoms)**: Nine DSM-IV-TR criterion symptom domains are evaluated to diagnose major depressive disorder (MDD). The Quick Inventory of Depressive Symptomatology (QIDS) provides an efficient assessment of these domains. We are using the Self Report version.
- **Jenkins Sleep Scale** (30 day measure so will skip week 2). Designed as an efficient and brief instrument for use in research, the four-item question evaluates the frequency and intensity of certain sleep difficulties in respondents. With only four items, it cannot begin to address the entire spectrum of sleep disorders and should only be considered for use as a preliminary screening device, and is therefore used in conjunction with PROMIS Sleep Disturbance.
- **Promis Sleep Disturbance:** The PROMIS-SD had greater measurement precision than the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) as indicated by larger test information values across the continuum of severity, despite having fewer total items, a major advantage for both research and clinical settings.[3]
- **COMBINE SAFTEE** (systematic assessment for treatment of emergent events modified for mental health and substance abuse)

The blue bar indicates shipment/delivery of the active or sham device.

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[1] Kroenke, Kurt; Spitzer, Robert L; Williams, Janet B W (2017-05-31). "The PHQ-9". Journal of General Internal Medicine. 16 (9): 606–613. doi:10.1046/j.1525-1497.2001.016009606.x. ISSN 0884-8734. PMC 1495268. PMID 11556941

[2] Löwe, Burnd; Spitzer; Gräfe; Kroenke; Quenter; Zipfel; Buchholz; Witte; Herzog (February 2004). "Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses". Journal of Affective Disorders. 78 (2): 131–140. doi:10.1016/s0165-0327(02)00237-9. PMID 14706723.

[3] A. John Rush, Ira H. Bernstein Development of short forms from the PROMIS™ sleep disturbance and Sleep-Related Impairment item banks, Behav Sleep Med. 2011 Dec 28; 10(1): 6–24.
doi: 10.1080/15402002.2012.636266 PMCID: PMC3261577 NIHMSID: NIHMS335121 PMID: 22250775

	Enroll	Baseline		2-Week	4-Week	8 Week
Inclusion/Exclusion	X					
Consent						
PHQ-8	X			X	X	X
Beck Depression Inventory	X			X	X	X
M.I.N.I Screen	X					
HAM-D	X				X	
Physician Telemedcine Visit	X				X	
Randomization	X					
Treatment Expectancy			X			
Instructions			X			
Quick Inventory of Depressive Symptomatology (QIDS-SR)		X		X	X	X
Jenkins Sleep Scale		X			X	X
Promis Sleep Disturbance		X		X	X	X
COMBINE SAFTEE				X	X	X
Final Feedback & Tolerability						X
Daily treatment adherence and adverse events						

Adverse Event Reporting & Medical Oversight

Licensed medical providers in the state in which the participant lives will provide medical oversight for this effort.

Adverse events will be collected qualitatively via customer support in the ProofPilot platform. In addition, medical oversight staff will automatically receive alerts if participants have a PHQ-8 score over 20 at the 2 week, 4 week or 8 week point. Those participants will also receive notifications to contact local medical support.

Participants will complete the COMBINE SAFTEE at the 2 week, 4 week and 8 week mark to provide additional data for safety and tolerability not otherwise collected.

All adverse events will be followed up upon and tracked in ProofPilot.

Participant Compensation

Participants may earn up to $100 for participation in the study.

- $10 Visa Gift Card for Baseline through completing first Fisher Wallace Treatment (aka 'Start Task') as identified above..
- $90 presented within 2 weeks of study completion (as defined by return of both the active and shame devices) based on the following:
    - $20 for each 2 week check in (up to $60)
    - Up to $30 as calculated by percentage of daily diaries completed over the 8 weeks